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Three-dimensional regions-of-interest-based intra-operative 4-dimensional soft tissue perfusion imaging using a standard x-ray system with no gantry rotation: A simulation study for a proof of concept

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Abstract

Purpose: Many interventional procedures aim at changing soft tissue perfusion or blood flow. One problem at present is that soft tissue perfusion and its changes cannot be assessed in an interventional suite because cone-beam computed tomography is too slow (it takes 4–10 s per volume scan). In order to address the problem, we propose a novel method called IPEN for Intra-operative 4-dimensional soft tissue PErfusion using a standard x-ray system with No gantry rotation.

Methods: IPEN uses two input datasets: (1) the contours and locations of 3-dimensional regions-of-interest (ROIs) such as arteries and sub-sections of cancerous lesions, and (2) a series of x-ray projection data obtained from an intra-arterial contrast injection to contrast enhancement to wash-out. IPEN then estimates a time-enhancement curve (TEC) for each ROI directly from projections without reconstructing cross-sectional images by maximizing the agreement between synthesized and measured projections with a temporal roughness penalty. When path lengths through ROIs are known for each x-ray beam, the ROI-specific enhancement can be accurately estimated from projections. Computer simulations are performed to assess the performance of the IPEN algorithm. Intra-arterial contrast-enhanced liver scans over 25 seconds were simulated using XCAT phantom version 2.0 with heterogeneous tissue textures and cancerous lesions. The following four sub-studies were performed: (A) The accuracy of the estimated TECs with overlapped lesions was evaluated at various noise (dose) levels with either homogeneous or

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heterogeneous lesion enhancement patterns.; (B) the accuracy of IPEN with inaccurate ROI contours was assessed; (C) we investigated how overlapping ROIs and noise in projections affected the accuracy of the IPEN algorithm; and (D) the accuracy of the perfusion indices was assessed.

Results: The TECs estimated by IPEN were sufficiently accurate at a reference dose level with the root-mean square deviation (RMSD) of $0.0027 \pm 0.0001 \text{ cm}^{-1}$ or 13 ± 1 Hounsfield unit (mean $\pm$ standard deviation) for the homogeneous lesion enhancement and $0.0032 \pm 0.0005 \text{ cm}^{-1}$ for the heterogeneous enhancement ($N=20$ each). The accuracy was degraded with decreasing doses: The RMSD with homogeneous enhancement was $0.0220 \pm 0.0003 \text{ cm}^{-1}$ for 20% of the reference dose level. Performing 3×3 -pixel averaging on projection data improved the RMSDs to $0.0051 \pm 0.0002 \text{ cm}^{-1}$ for 20% dose. When the ROI contours were inaccurate, smaller ROI contours resulted in positive biases in TECs, whereas larger ROI contours produced negative biases. The bias remained small, within $\pm 0.0070 \text{ cm}^{-1}$, when the Sorenson–Dice coefficients (SDCs) were larger than 0.81. The RMSD of the TEC estimation was strongly associated with the condition of the problem, which can be empirically quantified using the condition number of a matrix A_z that maps a vector of ROI enhancement values z to projection data and a weighted variance of projection data: a linear correlation coefficient (R) was 0.794 ($P < 0.001$). The perfusion index values computed from the estimated TECs agreed well with the true values ($R = 0.985$, $P < 0.0001$).

Conclusion: The IPEN algorithm can estimate ROI-specific TECs with high accuracy especially when 3×3 -pixel averaging is applied, even when lesion enhancement is heterogeneous, or ROI contours are inaccurate but the SDC is at least 0.81.

Keywords

Interventional radiology; x-ray system; soft tissue perfusion

1. Introduction

Images play an important role in interventional procedures that aim at changing tissue perfusion or blood flow. These procedures include endovascular mechanical thrombectomy^{1–3} for acute ischemic stroke and trans-arterial chemoembolization (TACE)^{4,5} and selective internal radiation therapy^{6–8} using yttrium-90 microspheres for liver tumor oncology. One problem at present is that soft tissue perfusion and its changes cannot be assessed in an interventional suite. If tissue perfusion could be assessed in real-time, prior to, during, or immediately after a core procedure is performed, it would allow for targeting a lesion more precisely (e.g., by injecting contrast agent prior to infusing drug and confirming the expected drug delivery sites for trans-arterial chemoembolization), minimizing the side effect (e.g., by assessing lung shunt fraction for yttrium-90 microspheres^{9,10}), assessing the change of perfusion quantitatively immediately after the procedure is completed, and performing an additional procedure if necessary. These are unmet clinical needs we plan to address ultimately.

Traditional diagnostic perfusion analyses allow for precise quantification of time-enhancement curves (TECs) on a voxel basis; however, perfusion analyses during an intervention do not have to be too sophisticated. Even obtaining one simple perfusion index

on a region basis can be invaluable for the intervention. For example, a time-to-peak enhancement index being “fast” (e.g., <6 sec for normal perfusion/blood flow), “moderate” (6–12 sec for penumbra or partially blocked), or “slow” (indicating infarct, blocked blood flow, or a bad catheter location).

An x-ray angiogram (two-dimensional projections) provides sub-second temporal resolution to capture blood flow (<0.3 sec/image) and a large field-of-view and coverage (30–40 cm), but it lacks volumetric information and has problems with overlapped regions. Flat-panel x-ray cone-beam computed tomography (CBCT)^{11,12} provides volume images but has a very limited temporal resolution (4–10 sec/image), a smaller field-of-view (25 cm), and strong motion artifacts. Attempts have been made to estimate soft tissue perfusion indices for stroke from a series of CBCT data and produced reasonably good results.^{13–17} Challenging issues may include a large computational expense, a large radiation dose, and insufficient accuracy and robustness. The use of a diagnostic multidetector-row computed tomography (CT) scanner on rails in an angio-suite has been investigated; however, the number of suites which are equipped with a CT scanner will remain limited because of a high equipment cost and a suboptimal workflow. The use of magnetic resonance scanners has similar issues.

We propose to develop a time-resolved **I**ntra-operative four-dimensional soft tissue **P**erfusion method using a standard x-ray system with **N**o gantry rotation (**IPEN**) (Fig. 1). IPEN is expected to achieve a sub-second temporal resolution (<0.3 sec/image), a large field-of-view (30–40 cm), a radiation dose comparable to one series of angiogram, and a smooth workflow; IPEN uses a single- or bi-plane, standard C-arm flat-panel x-ray system; thus, it requires no additional equipment cost. The innovation with IPEN is *not* to reconstruct volumetric images, because that is the source of problems with CBCT-based perfusion imaging. Instead, IPEN estimates TECs of multiple 3-dimensional regions-of-interest (ROIs) directly from x-ray projections acquired with no gantry rotation. Contours of ROIs will be obtained from pre-operative contrast-enhanced CT and ROIs include arteries, veins, sub-lesions of cancers, infarct and penumbra, and parenchyma directly next to the targeted area. The IPEN takes into account the patient motion and computes perfusion indices for each ROI such as time-to-peak and arterial blood volume.

Existing techniques such as “2D perfusion angiography,”^{18–21} “iFlow,”²² and similar methods²³ analyze temporal changes of pixel values on x-ray angiography images with blood vessels or an ROI. It may seem similar to the proposed IPEN superficially; however, there is a significant difference. While the proposed IPEN is based on the same concept as x-ray CT, the existing methods are essentially a qualitative analysis of x-ray projections; and due to the following inherent problems, they are only effective for vascular flow measurements^{18–20} and not suitable for soft tissue perfusion. First, the methods do not allow any overlaps in ROIs along x-rays. But lesions-of-interest for soft tissue perfusion analysis are often overlapped (see overlapping ROIs in Step 1, Fig. 1); therefore, they cannot perform soft tissue perfusion analysis. Second, they cannot take into account patient motion such as respiratory motion or head motion. Third, these methods ignore the ROI size along x-ray beams, and thus, they cannot tell if the entire tumor is enhanced or if only an anterior (or posterior) part of the tumor is enhanced. In contrast, IPEN can handle overlapped ROIs, take

into account patient motion and ROI sizes and shapes, and output quantitative perfusion indices for each ROI.

Computer simulations are performed to assess the basic performance of the IPEN algorithm in this study. The paper is structured as follows. In Section 2, we explain the IPEN algorithm in detail and outline computer simulation methods used in this study. We present the results in Section 3, discuss relevant issues in Section 4, and conclude the paper in Section 5.

2. Methods

We outline the proposed IPEN algorithm in Section 2.A. and computer simulation settings in Section 2.B.

2.A. IPEN algorithm

Let us briefly explain why IPEN works. If we know the thickness of an object that has an unknown but uniform linear attenuation coefficient, we only need one x-ray beam to estimate the attenuation coefficient. By extending the idea, N x-ray beams are sufficient in theory to estimate N ROI values even if ROIs are overlapped along x-ray beams as long as we can avoid the co-linearity (i.e., relative path lengths through ROIs being the same between x-ray beams). One x-ray projection image consists of more than a million ($= 1,000 \times 1,000$) pixels (or x-ray beams), which is sufficient to estimate 10–100 ROI values at each time point. It is a well-posed estimation problem even in the presence of noise and is expected to be computationally very robust. Some ROIs are offset with no overlap, and some ROIs have completely different TECs—for example, arteries will be enhanced in the first 5 s, followed by tumors, then liver parenchyma. Such spatial and temporal offsets will make the estimation even easier.

Once implemented, the workflow using the IPEN algorithm will consist of the following six steps (Fig. 1): (Step 1) Obtaining 3-dimensional ROIs from pre-operative CT images, (Step 2) determining the optimal scan protocol including the view angle and the radiation dose level, (Step 3) acquiring x-ray projection data, (Step 4) estimating and correcting for patient motion, (Step 5) estimating TECs of ROIs using the IPEN algorithm, and (Step 6) computing perfusion indices for ROIs. As the first study on the IPEN algorithm, we focused on Steps 2, 3, and 5 in this paper and used the following six assumptions: (i) All of the voxels inside an ROI have the same, homogeneous enhancement at any given time t ; (ii) the ROI contours (i.e., the shapes and positions) are accurate; (iii) there is no intra-scan patient motion such as respiratory motion; (iv) x-rays are mono-energetic; (v) there is no scattered radiation; and (vi) the detection efficiency is 100%. Assumption (ii) means that the ROIs drawn using pre-operative CT images are registered to x-ray projections. Note, however, that we do not use actual values of voxels; therefore, any changes in voxel values between pre-operative CT images and x-ray projections such as stomach contents will not affect the IPEN algorithm. Either volume-to-projection registration methods with pre-operative CT images^{24–31} or anatomical landmark-based methods^{32,33} can be used for Step 4. Inaccuracy in either Step 1 or Step 4 will result in inaccurate ROI contours, which will violate assumption (ii) and degrade the accuracy of the IPEN algorithm. In Studies A and B, the

performance of IPEN was assessed with cases that violated assumptions (i) and (ii), respectively (see Sections 2.B.1 and 2.B.2, respectively).

The assumptions (iv) and (v) were justified as follows. Note, however, that these assumptions are not inherent to the IPEN algorithm but were adopted as simplifying approximations used for this initial, proof of concept study. Approximating poly-energetic x-rays with mono-energetic x-rays at the effective energy of the x-ray spectrum is a standard technique that is sufficient for many applications. When a better quantitative accuracy is desirable for CBCT image reconstruction, a water-based beam hardening correction technique³⁴ is performed that normalizes the difference in effective energies across the x-ray projection images. It is very effective for the abdomen because the majority of attenuation is attributed to (water-like) soft tissues and will be used with IPEN.

A majority of scattered radiation is caused by the entire abdomen, and the scatter caused by the contrast enhancement is much smaller, likely less than 10% of the entire scatter, because line integrals increased by less than 10% due to the contrast enhancement (see Sec. 2.B.4). The proposed IPEN algorithm uses an average of a few projections acquired prior to the contrast enhancement as a part of the estimation (presented later in Eqs. (6) and (8)). These projections include both the attenuation and scatter that are attributed to the entire abdomen before contrast agent is injected. Therefore, most of the scatter is expected to be measured and eliminated from the estimation problem. In addition, scatter correction algorithms implemented in the x-ray system will further mitigate the effect of the scatter due to the enhancement.

Below we outline three major elements of the estimation algorithm: modeling, cost function, and optimization algorithm.

2.A.1. Data, object, and system modeling—We use bold letters to denote vectors or matrices in this paper. Let $\mathbf{x}_t = (x_{t,1}, \dots, x_{t,J})^T$, $0 \leq t \leq t_{end}$, be the linear attenuation coefficient of object voxels at time t , where J is the number of voxels and the operator $\mathbf{A}^T$ indicates a transpose of $\mathbf{A}$. We will start with $\mathbf{x}_0$ and eliminate it from the problem as outlined below. Let also $\mathbf{z}_t = (z_{t,1}, \dots, z_{t,I})^T$ be the ROI-specific enhancement at time t , where I is the number of ROIs. When the entire volume is divided into mutually exclusive ROIs with any voxel belonging to one of ROIs, and when all of the voxels inside any ROI have the homogeneous enhancement, the voxel value, i.e., the linear attenuation coefficient of voxel j , $x_{t,j}$, can be expressed by

$$x_{t,j} = x_{0,j} + z_{t,i}, \quad (1)$$

where $x_{0,j}$, is the pre-contrast-enhanced value of voxel j and the voxel j belongs to ROI i .

Cone-beam projections (line integrals) of the object $\mathbf{x}_t$, $\mathbf{y}_t = (y_{t,1}, \dots, y_{t,K})^T$, where K is the number of detector pixels, and the corresponding x-ray photon counts $\mathbf{n}_t = (n_{t,1}, \dots, n_{t,K})^T$ can be computed by

$$\mathbf{y}_t = \mathbf{A}_x \mathbf{x}_t = \mathbf{A}_x (\mathbf{x}_0 + \mathbf{A}_{z2x} \mathbf{z}_t) = \mathbf{A}_x \mathbf{x}_0 + \mathbf{A}_z \mathbf{z}_t, \text{ (with } \mathbf{A}_z = \mathbf{A}_x \mathbf{A}_{z2x} \text{)}, \quad (2)$$

$$\mathbf{n}_t = n_0 \exp(-\mathbf{y}_t), \quad (3)$$

where a projection matrix $\mathbf{A}_{z2x}$ maps the ROI value vector $\mathbf{z}_t$ to the voxel enhancement values and n_0 is the expected number of photons per detector pixel through the air.

The measured photon counts, $\tilde{\mathbf{n}}_t$, will be Poisson distributed:

$$\tilde{\mathbf{n}}_t \sim \text{Poisson}(\mathbf{n}_t) \quad (4)$$

from which the line integrals will be computed and stored as

$$\tilde{\mathbf{y}}_t = -\ln(\max(\tilde{\mathbf{n}}_t, \varepsilon)/n_0), \quad (5)$$

where ε is a small number to avoid $\ln 0$ and cap the line integrals to, e.g., 30 cm of water.

Assuming the absence of intra-scan motion, Eq. (2) can be approximated by an average of a few projections acquired prior to contrast enhancement, $\bar{\mathbf{y}}_0$:

$$\mathbf{y}_t \approx \bar{\mathbf{y}}_0 + \mathbf{A}_z \mathbf{z}_t. \quad (6)$$

2.A.2. Cost function—The cost function consists of a data fidelity term and a roughness penalty over time:

$$\Psi(\mathbf{z}) = L(\mathbf{z}) + \beta R(\mathbf{z}), \quad (7)$$

$$L(\mathbf{z}) = \frac{1}{2} \left\| \mathbf{y}(\mathbf{z}) - \tilde{\mathbf{y}} \right\|_{\mathbf{W}}^2 \approx \frac{1}{2} \left\| \mathbf{A}_z \mathbf{z} + \mathbf{y}_{bg} - \tilde{\mathbf{y}} \right\|_{\mathbf{W}}^2, \text{ (because Eq. (6))}, \quad (8)$$

$$R(\mathbf{z}) = \frac{1}{2} \sum_{t=0}^{t_{end}-1} \left\| \mathbf{z}_{t+1} - \mathbf{z}_t \right\|^2, \quad (9)$$

where $\mathbf{z} = (\mathbf{z}_0, \dots, \mathbf{z}_{t_{end}})$, $\mathbf{y} = (\mathbf{y}_0, \dots, \mathbf{y}_{t_{end}})$, $\tilde{\mathbf{y}} = (\tilde{\mathbf{y}}_0, \dots, \tilde{\mathbf{y}}_{t_{end}})$, $\mathbf{y}_{bg} = (\bar{\mathbf{y}}_0, \dots, \bar{\mathbf{y}}_0)$, β is the penalty strength parameter, and $\mathbf{W}$ is a statistical weighting by the inverse variance, approximated by the measurement.^{35–37} Note that the roughness penalty term does not encourage a smoothness between ROIs and that each ROI is treated independently.

2.A.3. Optimization algorithm—The cost function can be minimized with a non-negativity constraint using the separable paraboloidal surrogates (SPS) optimizer.^{35–37} The SPS approximates the Poisson likelihood by a quadratic function with an appropriate statistical weighting that is easier to minimize, and the SPS uses surrogate functions to separate all of the unknowns for ROIs and time frames such that they can be updated simultaneously.

$$\hat{\mathbf{z}} = \underset{\mathbf{z} \geq \mathbf{0}}{\operatorname{argmin}} \Psi(\mathbf{z}), \quad (10)$$

The pseudo code of the algorithm is presented in *Algorithm 1*.

Algorithm 1.	
Precompute and set	
$r = 1$	
$\mathbf{d} = \mathbf{A}_t^T [\mathbf{A}_t \mathbf{1} + \mathbf{c}]$	
$\mathbf{d}r = \mathbf{1} \oslash (\mathbf{d} + \beta r)$	
$\hat{\mathbf{z}} = \mathbf{0}$	
for iteration $l = 1, \dots, L$	
$\tilde{\mathbf{y}} = \mathbf{y}_d + \mathbf{A}_t \hat{\mathbf{z}}$	
$\mathbf{h} = \mathbf{c} + (\mathbf{y} - \tilde{\mathbf{y}})$	
$\mathbf{L} = \mathbf{A}_t^T \mathbf{h}$	
$\mathbf{R} = \mathbf{C}\mathbf{L}$	
$\hat{\mathbf{z}} = \max(\hat{\mathbf{z}} - (\mathbf{L} + \beta \mathbf{R}) + \mathbf{d}r, \mathbf{0})$	
end	
Definitions	
$\tilde{\mathbf{y}}$	Synthesized line integrals by forward-projected current estimate of ROI values $\hat{\mathbf{z}}$ and pre-enhanced line integrals
$\mathbf{y}$	Measured noisy line integral data
$\mathbf{y}_d$	An average of s raw measured projections acquired prior to contrast enhancement
$\mathbf{c}$	Precomputed curvature of data fidelity term, $c_{i,k} = \text{diag}(\mathbf{W}) = 1/\kappa_{i,k}$ (if $\kappa_{i,k} \neq 0$) or $1/\epsilon$ (if $\kappa_{i,k} = 0$)
$\mathbf{L}$	Derivatives of data fidelity term surrogate for ROI values $\hat{\mathbf{z}}$
$\mathbf{d}$	Curvature of data fidelity term surrogate for ROI values $\hat{\mathbf{z}}$
$\mathbf{R}$	Derivatives of penalty surrogate for ROI values $\hat{\mathbf{z}}$
$\mathbf{r}$	Curvature of penalty surrogate for ROI values $\hat{\mathbf{z}}$
$\mathbf{1}, \mathbf{0}$	A vector for ROI values with all 1's and 0's, respectively

where operators $\circ$ and $\oslash$ are the Hadamard (element-wise) product and division, respectively, $\mathbf{C}$ is the differencing operator [Eq. (9)], and $\mathbf{1}$ and $\mathbf{0}$ are vectors with all 1's and 0's, respectively.

2.B. Computer Simulation settings

We outline the common settings including phantoms, liver cancer lesions, x-ray projections, and parameters for IPEN, and data analysis methods in Sec. 2.B.1. Settings and data analysis methods specific to sub-studies A–D will be explained in Sections 2.B.2–2.B.5, respectively.

2.B.1. Common settings—The following common settings and assumptions (i)–(vi) outlined at the beginning of Sec. 2.A were used for this study unless otherwise noted.

XCAT phantom: We used the 4-dimensional extended NURBS-based cardiac-torso (XCAT) phantom^{38,39} version 2.0 (male, 50th percentile characteristics of body size and organ masses, no motion, arm down) and generated CT images at 60 keV with a matrix size of $600 \times 600 \times 600$ with a voxel size of $(1 \text{ mm})^3$. Smooth heterogeneous background tissue texture with standard deviation of 0.003 cm^{-1} or 15 Hounsfield unit (HU) was added using uniform random numbers ranging over $\pm 0.0607 \text{ cm}^{-1}$ followed by a $5 \times 5 \times 5$ boxcar smoothing filtering (Fig. 2).⁴⁰ Intra-arterial contrast-enhanced liver scans were simulated, which enhanced the hepatic arteries and lesions outlined below.

Cancerous lesions: Fifteen spiculated lesions with different shapes and sizes (see Fig. 2) were created using the same method as outlined in Ref.⁴¹. The mean and the standard deviation of the lesion volume sizes were $40.3 \pm 9.6 \text{ ml}$ and the range was 24.4–61.9 ml.

X-ray projections: A flat panel detector with $1,000 \times 1,000$ pixels with the projected pixel size of $(0.5 \text{ mm})^2$ [hence, the detector area of $(50 \text{ cm})^2$] at the iso-center and 100% detection efficiency was used. The x-ray source-to-iso-center distance was 60 cm and the iso-center-to-detector distance was 20 cm. Cone-beam projection data (line integrals, $\mathbf{y}_l$) were generated using ASTRA toolbox^{42,43} version 1.9.0.dev11 and a graphics processing unit (GPU). Noisy projection data $\tilde{\mathbf{y}}_l$ (see Fig. 2) were computed from $\mathbf{y}_l$ by converting line integrals to photon counts and adding Poisson noise using Eqs. (3)–(5). The other parameters were as follows: the frame rate, 5 frames/s; $t_{\text{end}} = 25 \text{ s}$; view angle, the anterior–posterior direction ($\varphi = 0^\circ$);

$n_0=10^4$ photons/detector pixel [Eq. (5)]; and $e=1$ photons/pixel [Eq. (5)]. The image noise levels with $n_0=10^4$ appeared to be similar to image noise levels of clinical abdominal x-ray angiography (i.e., the standard deviation of ~5% of the mean value) and $n_0=10^4$ is called the reference dose in this paper. The entrance energy and dose to the phantom per projection with $n_0=10^4$ at 60 keV computed using sepctr software⁴⁴ were 0.21 mR and 1.93 μ Gy, respectively, whereas those with polychromatic x-rays with 100 kVp, 10 mA, 1 ms per projection were 0.38 mR and 3.40 μ Gy, respectively.

IPEN: The projector A_z was computed by ASTRA toolbox using a GPU prior to the iteration, while iteration was performed by a central processing unit (CPU). The TECs of arteries, lesions, and the background over 126 frames were estimated using the following parameters: $\beta=0.001$ [Eq. (7)]; the number of iteration, $L=300$ (**Algorithm 1**); and the initial estimate of z was zeros.

Data analysis: A measure of the goodness of the estimated TECs was the root-mean-square deviation (RMSD) from the true TECs from $t=0$ s to 16 s of all of the ROIs including the one for the background, i.e., the rest of the body.

$$RMSD = \left(\int_{t=0}^{16} dt \sum_{i=1}^{N_i} \|\hat{z}_{t,i} - z_{t,i}\|^2 / N_i \right)^{\frac{1}{2}}, \quad (11)$$

where N_i is the number of ROIs used in computation. The target RMSD was 0.0070 cm^{-1} , which is 15% of the averaged TEC values.

2.B.2. Study A on basic performance—The following specific settings were used to assess the basic performance of the IPEN algorithm with overlapped lesions, at four different noise (dose) levels, with either homogeneous or heterogeneous lesion enhancement patterns, and with or without a noise reduction scheme.

Phantoms, TECs, enhancement patterns: Twenty XCAT phantoms with heterogeneous tissue texture were used. For each phantom, three lesions were randomly chosen from the 15 cancerous lesions and inserted into the liver. Lesion 1 had two tissue classes (or two sub-sections), a thin rim and a core (Fig. 2A), created by morphological erosion and dilation operations; lesion 2 had two spatial sub-regions, the anterior part and the posterior part, split by a plane with a polar angle (θ , shown later in Fig. 7) of 45 degrees; lesion 3 had neither of these sub-divisions. Lesion 1 simulated a scenario of overlapping sub-sections with different viabilities, lesion 2 simulated a scenario when a part of a tumor had a different feeding artery. TECs of each of the sub-lesions and arteries will be presented later in Fig. 4 and examples of noisy projections are presented in Figs. 2E–2H. The lesions were enhanced either homogeneously (Figs. 2A–2B) or heterogeneously (Figs. 2C–2D); the heterogeneous enhancement was realized by scaling the enhancement by $(1+r)$, where r was generated by uniformly-distributed random numbers ranging over ± 12.14 followed by a $5 \times 5 \times 5$ boxcar smoothing filtering, resulting in a standard deviation of 30% of the expected enhancement among voxels. Each phantom was scanned once under each of the investigated settings.

X-ray projections: Four different initial exposure levels (n_0) were used: 1×10^3 , 2×10^3 , 5×10^3 , 1×10^4 photons/detector pixel.

IPEN: There were seven ROIs in total used in the estimation: one for arteries, five for cancerous lesions and their sub-sections, and one for background. The IPEN was performed twice on each dataset: once without any additional pre-processing, and the second time, after 3×3 -pixel averaging performed on noisy projection data $\tilde{y}_i$ prior to the TEC estimation. The 3×3 -pixel averaging was employed in order to address problems with noisy data, which will be presented in Sec. 3.

Data analysis: There were 16 settings ($=4$ noise/dose levels $\times 2$ for homogeneous or heterogeneous lesion enhancement $\times 2$ with or without pixel binning) $\times 20$ phantoms. An RMSD value was computed for each scan from seven ROIs over the first 16 s (80 time frames) and the mean and the standard deviation of RMSDs over 20 phantoms were computed for each setting. A paired-sample two-tail Student's t -test was performed to assess if the difference between different settings was statistically significant. A P value less than 0.01 was considered significant.

2.B.3. Study B on inaccurate ROI contours—The following specific settings were used to evaluate the effect of inaccurate ROI contours.

Phantom and scans: One phantom with two lesions, lesion 2 and lesion 3 used in Study A with no sub-lesions, was scanned 10 times. The two lesions were not overlapped in projections (see Figs. 2F and 2G).

IPEN and ROI contours: For both of the two lesions, the ROI contours used in IPEN estimation were created by applying morphological operations to the true ROI contours, either erosion or dilation multiple times at the maximum of six times, resulting in thirteen different ROI contours in total. The smallest ROIs were produced by repeating erosion six times and the total volume of the two created ROIs relative to that of the two true ROIs was 0.28 and a Sorensen–Dice Coefficient (SDC) between the created and the true ROIs was 0.28. The largest ROIs, produced by repeating dilation six times, had a relative volume of 3.21 and an SDC of 0.31. Examples of created ROIs will be presented later in Fig. 5.

Data analysis: There were datasets for 13 ROI contours $\times 10$ scans. A bias value was computed from four ROIs (arteries, two lesions, and background) over the first 16 s (80 frames) for each scan, and the mean and the standard deviation of biases over 10 scans were computed for each ROI contour setting.

2.B.4. Study C on problem condition—In theory, the problem setting for the IPEN algorithm could be ill-posed, if two or more ROIs had the same ratio of path lengths for all of the x-ray beams passing through the ROIs. It would be impossible to estimate the enhancement for each ROI. However, ROI contours are obtained not from geometrical shapes but from biological lesions with complex shapes presented in pre-operative contrast-enhanced CT images; therefore, it is practically impossible for the problem to become ill-posed.

In practice, the problem can be ill-conditioned when ROIs are overlapped or data are noisy and biased. We wish to quantify the degree of ill-conditionedness and compute resulting errors. One may attempt to use singular values of the projection matrix A_z that maps an ROI enhancement vector to a projection data vector. There are, however, a few problems that make this approach challenging. First, the projection matrix A_z does not include the unenhanced object x_0 , which is the major cause of noise in projections (discussed below). Second, as it will be presented in Section 3, larger noise in projections may result in bias in the estimated TECs, due to both a non-linearity of logarithm operation and a Gaussian approximation of a Poisson distribution. A linear projection cannot model these non-linear effects and resulting biases.

We propose an empirical index called ill-conditionedness index (ICI) to quantify the degree of ill-conditionedness of a given problem with IPEN:

$$ICI \equiv \alpha_1 [CN(A_z)]^2 + \alpha_2 var((A_z \mathbf{1})^o(\tilde{y}_0 - y_0)) + \alpha_3, \quad (11)$$

where $CN(\bullet)$ returns the condition number of the input matrix, $var(\bullet)$ returns the variance of the input vector, $\mathbf{1}$ is a vector with all 1's, and α_1 , α_2 , and α_3 are parameters to balance the contribution of the two terms and scale and offset the two terms to improve the numerical agreement to the quality index such as an RMSD of TECs. The ICI is based on the three elements of the data fidelity term, Eq. (8), and allows us to study the effect of the two aspects of the projections—the overlap between ROIs in A_z and the bias induced by the noise of projections $\tilde{y}$ —separately. The first term concerns the condition number of the projection matrix for ROI values, A_z . The second term uses weighted projection data measured through an unenhanced volume at $\tilde{y}_0$, rather than enhanced volumes. The effect of contrast enhancement on the noise variance would be secondary as the attenuation due to the patient's entire body was the dominant factor. For example, the line integrals increase by less than 10% due to the contrast enhancement.

We used the three different settings outlined below, first, to examine each of the two terms individually (settings C1 and C2), and then, to assess the two terms combined (setting C3).

Setting C1: The same XCAT phantom with the two lesions as Study B was used. Each of the two lesions was split into two sub-sections by a plane with a polar angle (θ , presented later in Fig. 8D) changing from 0° (i.e., the largest and worst condition number) to 90° (i.e., the smallest and best condition number) with an increment of 5° . Ten scans were performed for the phantom with each splitting polar angle, and there were datasets for 19 angles $\times$ 10 scans in total.

Setting C2: The same XCAT phantom with two lesions as setting C1, with the polar angle of $\theta=20^\circ$ was used. The x-ray dose levels were changed from $n_0=10^3$ photons/detector pixel to $n_0=10^4$ photons/pixel, by an increment of 10^3 photons/pixel. The phantom was scanned ten times at each dose level and there were datasets for 11 noise levels $\times$ 10 scans in total.

Setting C3: The same XCAT phantom with two lesions as setting C1, with the polar angle of $\theta=0^\circ$ was used. The view angle (ϕ , presented later in Fig. 8D) was changed from 0° (the

anterior–posterior direction) to 90° (the lateral direction) with an increment of 5° . Note that increasing φ improved the condition of the projector A_z . In contrast, as the number of initial photons n_0 remained constant, increasing φ resulted in noisier projections, because the attenuation within the body increased as the effective thickness of the body increased. Therefore, there would be a tradeoff between the two factors. Ten scans were performed at each view angle and there were datasets for $19 \text{ angles} \times 10 \text{ scans}$ in total.

Data analysis: An RMSD was calculated for each scan from six ROIs (arteries, four sub-sections, and background) over the first 16 s (80 frames); and the mean and the standard deviation of RMSDs over 10 scans were computed for a given condition. The condition number of A_z for five ROIs (excluding the background ROI) was computed using the ROI contours and a view angle φ . The variance of weighted noisy projections was computed using the footprint of the five ROIs. The three ICI parameters were estimated by maximizing the agreement between the RMSD values and the ICI values using data for settings C1 and C2, which were then applied to data for settings C3 with no adjustment. The mean and the standard deviation of ICI values over 10 scans for a given condition were computed. Finally, a linear correlation coefficient (R) between RMSD values and ICI values was computed for each of the three settings.

2.B.5. Study D on perfusion analyses for TACE—The following specific settings were used to evaluate the accuracy of simple perfusion indices computed from the estimated TECs before and after a TACE treatment.

Phantoms: There were two sets of phantoms, one for pre-TACE and the other for post-TACE (Fig. 3). The pre-TACE phantoms were the twenty XCAT phantoms with the heterogeneous lesion enhancement used in Study A, with an additional enhancement in the liver parenchyma up to 0.05 cm^{-1} (or 240 HU). The post-TACE phantoms were the same as the pre-TACE phantoms with different baseline values and TECs for cancerous lesions and sub-sections.

Embolization materials infused to lesions during the TACE procedure contain contrast agent. Thus, the baseline voxel values for ROIs of the post-TACE phantom were set higher than those for the pre-TACE phantom and were created as follows. An offset value $d_1 \text{ cm}^{-1}$, $0 < d_1$, for an ROI was determined by normally-distributed random numbers with a mean of 0.05 cm^{-1} (or 238 HU) and a standard deviation of 0.05 cm^{-1} (or 240 HU), which was clipped at 0 cm^{-1} . Heterogeneous offset values for voxels within the ROI was generated using d_1 and the method outlined in Sec. 2.B.2, which were added to the baseline voxel values for the pre-TACE phantom.

The TEC for the post-TACE ROI was created by scaling the TEC for the pre-TACE ROI by d_2 , $0.1 < d_2 < 1.0$, for a weaker enhancement than the pre-TACE and shifting it along time by $d_3 \text{ s}$, $0 < d_3 < 5$, for a delayed enhancement. The scaling parameter d_2 was generated by normally-distributed random numbers with a mean of 0.4 and a standard deviation of 0.2, which was clipped at 0.1 and 1.0. The time delay parameter d_3 was generated by uniformly-distributed random numbers ranging from 0 s to 5 s, which was rounded to the nearest projection times.

IPEN: There were eight ROIs in total used in the estimation: one for arteries, five for cancerous lesions and their sub-sections, one for liver parenchyma, and one for background. The 3×3-pixel averaging was employed prior to the TEC estimation.

Perfusion indices: The following two indices were computed for each ROI from both the true TEC and the estimated TEC. A first perfusion index was time-to-peak, which was time from the start of the contrast injection to the peak of the TEC. A second perfusion index was the maximum slope of the TEC, which we call *max-slope* in this paper. These indices reflect the effect of the time delay and scaling, respectively. The index values obtained with the true TEC are called the true index values.

Data analysis: There were 320 TECs (=8 ROIs × 20 phantoms × 2 scans) in total. An RMSD was calculated for each scan from eight ROIs (arteries, five sub-sections, liver, and background) over the first 16 s (80 frames); the mean and the standard deviation of RMSDs over 20 phantoms were computed for pre-TACE and post-TACE separately. There were 200 measurements (=5 sub-sections × 20 phantoms × 2 scans) each for the time-to-peak and max-slope. An RMSD for each index was calculated for each phantom with 5 sub-sections; the mean and the standard deviation of RMSDs over 20 phantoms were computed for pre-TACE and post-TACE separately. A linear correlation between the true and estimated values was computed, and the slope and the y-intercept of the regression line was obtained. A *P* value less than 0.01 was considered significant.

3. Results

3.A. Study A on basic performance

Figure 4 shows the true and estimated TECs with homogeneous lesion enhancement at four different dose/noise levels. At the reference dose level, $n_0=10^4$ photons/pixel (Fig. 4A), the estimated TECs for all of lesions and sub-lesions appeared very accurate with small biases; the mean±standard deviation of RMSD was $0.0027\pm0.0001\text{cm}^{-1}$, (Table 1), which was significantly below the target RMSD at 0.0070 cm^{-1} (determined in Sec. 2.B.1). Biases increased with decreasing dose levels (Figs. 4B–4D); the RMSD was $0.0062\pm0.0002\text{ cm}^{-1}$ for 50% of the clinical dose level, $0.0220\pm0.0003\text{ cm}^{-1}$ for 20% dose, and $0.0412\pm0.010\text{ cm}^{-1}$ for 10% dose. Notice that the standard deviation of RMSDs was very small. Positive biases were due to the positive biases in $\tilde{y}_i$, which were caused by both the logarithm operation being performed on very small number of photon counts $\tilde{n}_i$ in Eq. (5)⁴⁵ and the Poisson noise–Gaussian function mismatch.

The accuracy of the estimated TECs were very similar even with heterogeneous lesion enhancement (see Table 1). The RMSD values were very close to the cases with homogeneous lesion enhancement; the absolute differences were equal to or less than 0.0005 cm^{-1} and 0.0007 cm^{-1} for without and with the 3×3-pixel averaging (see the next paragraph for the 3×3-pixel averaging), respectively. The difference was statistically significant in some cases; however, the difference itself was small in general. It shows that the proposed IPEN remains functional in spite of the heterogeneity of lesion enhancement, which violates the fundamental assumption in Eq. (1). This was probably because the effect of local

heterogeneity onto measured line integrals over lesions was limited and many detector pixels were used to estimate the enhancement of each lesion, which further suppressed the effect of the local heterogeneity.

Figure 5 shows the true and estimated TECs from the same projection data used for Fig. 4, but with 3×3 -pixel averaging performed on projection data prior to applying the IPEN algorithm. Table 1 presents that the use of 3×3 -pixel averaging improved the RMSDs significantly for all of the noise/dose levels and for both homogeneous and heterogeneous lesion enhancement. The relative improvement was as much as 44.3%–77.4% and statistically significant (right two columns, Table 2). The results showed that even though it is an empirical method, the 3×3 -pixel averaging was effective in decreasing the effect of the fewer photon counts. With 3×3 -pixel averaging, the RMSD values of IPEN were within the target goal of 0.0070 cm^{-1} up to 20% of clinical dose level for both homogeneous and heterogeneous lesion enhancement patterns (Table 1).

It took 40–50 s to execute 300 iterations using a CPU with 1.25GHz and 16 GB memory. We continued the iteration up to 10^4 iterations to confirm that the changes in TECs after 300 iterations were very small ($<10^{-6}\text{ cm}^{-1}$).

3.B. Study B on inaccurate ROI contours

Figure 6 plots the biases against either relative volumes (Fig. 6A) or SDCs (Fig. 6B). The estimated TECs had positive biases when ROI contours used in the estimation were inaccurately smaller than the true contours, whereas there were negative biases with inaccurately larger contours. It can also be seen that the absolute bias was within $\pm 0.0070\text{ cm}^{-1}$ if the relative volume (r_{vol}) was in the range of 0.81–1.56. The corresponding SDCs were 0.81 (when smaller ROIs were used) and 0.64 (when larger ROIs were used), which seem to be a reasonable target, as many automatic image segmentation methods in the literature reported SDCs of 0.9 or higher.^{46–48}

The mean of the estimated TECs with the smallest, the accurate, and the largest ROIs are presented in Fig. 7. The following observations were made: (1) There was no bias-cancelling effect between ROIs; (2) when the two lesions had non-zero enhancement for $t > 3\text{ s}$, the artery ROI had positive (negative) biases when the two lesions had positive (negative) biases; and (3) the TEC of the background ROI hardly changed. The mean TEC values were 0.00017 cm^{-1} or 0.8 HU with the accurate ROI contours, 0.00024 cm^{-1} or 1.1 HU with the smallest ROI contours, and 0.00016 cm^{-1} or 0.8 HU with the largest ROI contours.

3.C. Study C on problem condition

The obtained ICI parameters in Eq. (11) were $\alpha_1=1.66\times 10^{-4}$, $\alpha_2=1.32\times 10^{-1}$, and $\alpha_3=-8.90\times 10^{-4}$. When the polar angle θ used for creating two sub-sections (see Fig. 8D) was small in setting C1, the difference between two sub-sections was decreased—that is, one sub-section had a positive bias, while the other sub-section had a negative bias—while the sum of the values of the two sub-sections remained the same. Figure 8A shows the RMSDs, the condition numbers of A_z , and the ICI values plotted against the polar angle θ . The three data curves agreed with each other very well qualitatively as well as quantitatively: The

correlation coefficient (R) was 0.969 ($P<0.001$) between the RMSDs and the condition number, and 0.994 ($P<0.001$) between the RMSDs and ICIs.

When noise was large in setting C2, all of TECs had positive biases, as seen in Figs. 4B–4D. Figure 8B presents the RMSDs, the weighted variance of projections, and the ICI values plotted over the number of initial photons n_0 . The three data curves were in good agreements: The correlation coefficient was 0.995 ($P<0.001$) between the RMSDs and the weighted data variance, and 0.995 ($P<0.001$) between the RMSDs and ICIs.

Figure 8C shows the results of setting C3: The RMSDs, the weighted variance of projections, scaled condition numbers of A_z , and the ICI values were plotted against the view angle ϕ (see Fig. 8D). The condition numbers improved monotonically with increasing ϕ , whereas the variance of data worsened in general with increasing ϕ . The variance did not change smoothly due to strong local attenuation by bones (i.e., spine and arms). The RMSD values and the ICI values showed similar trends, decreasing first until $\phi=25^\circ$ then increasing to $\phi=60^\circ$. The correlation coefficient between the RMSDs and ICIs was strong at 0.794 ($P<0.001$).

3.D. Study D on perfusion analyses for TACE

The mean and standard deviation of parameter values for post-TACE phantoms were $0.0245\pm0.0380\text{ cm}^{-1}$ or $117\pm181\text{ HU}$ (range, 0.0000–0.1591 cm^{-1} or 0–758 HU) for the offset enhancement parameter d_1 , 0.20 ± 0.25 (range, 0.00–1.00) for the scaling parameter d_2 , and $1.27\pm1.69\text{ s}$ (range, 0.00–4.80 s) for the time delay parameter d_3 . The mean and the standard deviation of RMSDs over 20 phantoms of the estimated TECs were $0.0021\pm0.0006\text{ cm}^{-1}$ for pre-TACE cases and $0.0011\pm0.0003\text{ cm}^{-1}$ for post-TACE cases; and these values were comparable to the results of Study A without liver parenchyma enhancement with heterogeneous enhancement with 3×3 -pixel averaging ($0.0018\pm0.0004\text{ cm}^{-1}$).

The mean and standard deviation of the true time-to-peak values were $6.76\pm1.79\text{ s}$ (range, 3.80–8.60 s) for pre-TACE phantoms and $9.29\pm2.38\text{ s}$ (range, 4.00–13.40 s) for post-TACE phantoms; and those for the max-slope values were $0.060\pm0.044\text{ cm}^{-1}\text{ s}^{-1}$ (range, 0.026–0.147 $\text{cm}^{-1}\text{ s}^{-1}$) for pre-TACE phantoms and $0.023\pm0.023\text{ cm}^{-1}\text{ s}^{-1}$ (range, 0.003–0.122 $\text{cm}^{-1}\text{ s}^{-1}$) for post-TACE phantoms. The accuracy of the two perfusion index values was comparable between pre- and post-TACE: The RMSD of the time-to-peak index values for all of ROIs was $0.31\pm0.14\text{ s}$ (range, 0.13–0.57 s) for pre-TACE and $0.45\pm0.20\text{ s}$ (range, 0.13–0.85 s) for post-TACE; and the RMSD of the max-slope values was $0.003\pm0.001\text{ cm}^{-1}\text{ s}^{-1}$ (range, 0.001–0.006 $\text{cm}^{-1}\text{ s}^{-1}$) for pre-TACE and $0.003\pm0.001\text{ cm}^{-1}\text{ s}^{-1}$ (range, 0.001–0.006 $\text{cm}^{-1}\text{ s}^{-1}$) for post-TACE. Figure 9 plots the estimated perfusion index values against the true index values. The linear correlation coefficient was 0.985 ($P<0.0001$; regression line, $y=0.97x+0.02$) for the time-to-peak and 0.998 ($P<0.0001$; regression line, $y=1.00x+0.00$) for the max-slope.

4. Discussion

Study A has demonstrated that the proposed IPEN algorithm can estimate TECs of overlapped lesions, with high accuracy (i.e., RMSDs $<0.0070\text{ cm}^{-1}$) from projections

acquired with no gantry rotation at a clinical dose level. The temporal regularization parameter β was very small (1×10^{-3}) and played a very limited role in this study because the lesion size was sufficiently large such that there were a large number of detector pixels under the footprint of the lesion. The statistical power of the estimation for each time frame was sufficiently large, which resulted in small standard deviations in the estimated TECs and RMSDs. We think that the temporal regularization may be more effective when ROIs are smaller. Alternatively, we can set $\beta=0$ and estimate z_t for each time t independently. It will decrease the number of unknowns for each estimation significantly (e.g., from 7 ROIs $\times$ 126 frames to 7 for Study A), which may allow us to use even more computationally efficient algorithms and parallel computing. The non-negativity constraint was not the cause of biases with lower doses in this study; biases remained the same even if the constraint was removed.

The IPEN was functional even at lower dose levels; however, the RMSDs increased as the dose was lowered. The 3×3 -pixel averaging was found to be very effective, decreasing the RMSD under the target accuracy level ($< 0.0070 \text{ cm}^{-1}$) for cases with 20% or 50% of the reference dose. The 3×3 -pixel averaging was chosen for its simplicity, but other options can be used. For example, the kernel can be changed to $3 \times 3 \times 3$ or the algorithm can be adaptive and non-linear. The effectiveness of noise reduction schemes may also depend on the data form the x-ray system saves projection data, i.e., x-ray intensities ($\tilde{n}_t$) or line integrals ($\tilde{y}_t$) or other forms. We will revisit the noise reduction scheme when we perform phantom or animal studies with a physical x-ray system.

Study C has shown that when each factor was studied separately, both the condition number of the projector A_z and the weighted noise variance of projections had very good correlations with the RMSD ($R=0.969$ and 0.995 , respectively) and that the proposed ICI had a strong correlation with the RMSD when the two factors were changed simultaneously ($R=0.794$). It implies that when a patient's pre-operative CT images are obtained and ROI contours are determined, one may be able to predict the expected RMSD using the ICI. Furthermore, one may be able to optimize scan protocols such as the view angle (φ), the dose level (n_0), and the frame rate, and adjust a way to draw multiple lesion contours within the scope of the scan and analysis, in order to meet the target RMSD. We envision that the pre-operative planning will be performed similarly to radiation therapy planning.

We have studied cases when some of the assumptions are violated. The accuracy of IPEN was affected very little when lesion enhancement was heterogeneous, not homogeneous (Study A). The IPEN remained sufficiently accurate even when ROI contours were inaccurate, as long as the SDC was larger than 0.81 (Study B). Note, however, that the inaccurate ROI contours studied in this paper were typical but simple cases and further studies are necessary. Multiple lesions may exchange biases and errors between them when their ROI contours are inaccurate and they are overlapped along x-ray paths. The "communication" mechanism seems complex. Larger or smaller ROIs may result in a different level of errors at the same SDC and a misplacement of ROIs will also result in errors. We shall study all of them systematically in the future.

In Study D, we simulated simple perfusion analyses performed before and after TACE procedures. The perfusion index values computed from the estimated TECs by IPEN were in

excellent agreement with the index values computed from the true TECs, in spite of the additional enhancement in the liver parenchyma for both pre- and post-TACE cases and the enhancement in lesions at $t=0$ for post-TACE cases.

One may wonder if slowly rotating gantry during the data acquisition and changing view angles may be better. We think that not rotating the gantry will not only make the clinical workflow easier but also make IPEN more accurate. When the optimal view angle is predicted as discussed above, acquiring projection data from the optimal angle will minimize the error. In addition, if the patient moves during the scan, it will be easier to detect the motion if the gantry is not moving.

Several ROI-based algorithms have been proposed previously. Huesman⁴⁹ proposed to estimate ROI-specific values directly from projections without reconstructing images. He swapped the order of image reconstruction and image analysis such that the ROI values can be computed directly from projections. Carson⁵⁰ used ROIs with uniform values to represent the image and used the maximum-likelihood algorithm to estimate ROI values. Some of Carson's findings on ROIs were similar to ours: "sizing errors are more significant than offsets or nonhomogeneity." Du, *et al.*,^{51,52} used a mixture of ROIs and voxels to represent an image volume in order to improve the statistical power of ROI value estimation. Xu, *et al.*,⁵³ also used ROIs and voxels to represent images in order to have a unique solution to the interior image reconstruction problem. The above methods, except Carson's, work only when projections over 180° or 360° (i.e., the angular range necessary to complete voxel-based tomography of the object) are available. In contrast, the gantry does not have to rotate for IPEN, because IPEN takes a full advantage of homogeneity in ROI enhancement; and therefore, x-ray beams from one projection angle are sufficient for the estimation. In addition, in order to make the use of homogeneity a realistic assumption, heterogeneous pre-contrast voxel values were removed from the estimation problem by using pre-contrast-enhanced projection data and the homogeneity was applied only to enhanced lesions (or sub-sections).

The study had several limitations. First, x-rays were not poly-energetic but mono-energetic and x-ray scatter was not simulated. The justifications for these assumptions have been provided in Sec. 2.A. We plan to assess their effects in future studies using an actual x-ray system and physical phantom measurements. Second, the detection efficiency was 100% and no energy weighting was applied. We will need to carefully examine these using a physical x-ray system. Third, simulated heterogeneous lesion enhancement patterns appear similar to those observed in clinical cases; however, they were not quantitatively validated. Fourth, the two perfusion indices used in this study, the time-to-peak and the max-slope, were very simple ones. Further studies are warranted to investigate other indices suitable for intra-operative soft tissue perfusion measurements. We shall leave it to the future work. Finally, this study focused on the fundamental part of the IPEN algorithm and the core elements in the expected workflow: Step 2 (Optimal scan protocols), Step 3 (x-ray projections), and Step 5 (TEC estimation by IPEN). The other two steps in the workflow, i.e., Step 1 (ROI segmentations) and Step 4 (patient motion), have been deferred to future studies, while a preliminary study on Step 6 (perfusion analysis) has been performed. Given the extensive

literature on these steps, we believe that it was a reasonable decision as the first paper on the IPEN algorithm and plan to tackle them one by one in future work.

5. Conclusion

The proposed IPEN algorithm is able to estimate TECs of overlapped lesions using a standard x-ray system without gantry rotation. The study has demonstrated that the proposed IPEN functions with sufficient accuracy robustly with heterogeneous lesion enhancement, lower doses, and inaccurate ROI contours of SDC up to 0.81.

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References

1. Papanagiotou P, Ntaios G. Endovascular Thrombectomy in Acute Ischemic Stroke. *Circulation: Cardiovascular Interventions*. 2018;11(1):e005362. [PubMed: 29311286]
2. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 h with selection by perfusion imaging. *New Engl J Med*. 2018;378:708. [PubMed: 29364767]
3. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *New England Journal of Medicine*. 2018;378(1):11–21.
4. Reyes DK, Vossen JA, Kamel IR, et al. Single-Center Phase II Trial of Transarterial Chemoembolization With Drug-Eluting Beads for Patients With Unresectable Hepatocellular Carcinoma: Initial Experience in the United States. *The Cancer Journal*. 2009;15(6):526–532. [PubMed: 20010173]
5. Geschwind JF. Chemoembolization for hepatocellular carcinoma: where does the truth lie? *J Vasc Interv Radiol*. 2002;13(10):991–994. [PubMed: 12397119]
6. Stubbs RS, Wickremesekera SK. Selective internal radiation therapy (SIRT): a new modality for treating patients with colorectal liver metastases. *HPB : the official journal of the International Hepato Pancreato Biliary Association*. 2004;6(3):133–139. [PubMed: 18333066]
7. Stubbs RS, Cannan RJ, Mitchell AW. Selective internal radiation therapy with 90yttrium microspheres for extensive colorectal liver metastases. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2001;5(3):294–302. [PubMed: 11360053]
8. Gray B, Van Hazel G, Hope M, et al. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2001;12(12):1711–1720. [PubMed: 11843249]
9. Ludwig JM, Ambinder EM, Ghodadra A, Xing M, Prajapati HJ, Kim HS. Lung Shunt Fraction prior to Yttrium-90 Radioembolization Predicts Survival in Patients with Neuroendocrine Liver Metastases: Single-Center Prospective Analysis. *Cardiovascular and interventional radiology*. 2016;39(7):1007–1014. [PubMed: 26964779]
10. Narsinh KH, Buskirk MV, Kennedy AS, et al. Hepatopulmonary Shunting: A Prognostic Indicator of Survival in Patients with Metastatic Colorectal Adenocarcinoma Treated with 90Y Radioembolization. *Radiology*. 2017;282(1):281–288. [PubMed: 27440733]
11. Lauritsch G, Boese J, Wigstrom L, Kemeth H, Fahrig R. Towards cardiac C-arm computed tomography. *Medical Imaging, IEEE Transactions on*. 2006;25(7):922–934.

12. Wallace MJ, Murthy R, Kamat PP, et al. Impact of C-arm CT on Hepatic Arterial Interventions for Hepatic Malignancies. *Journal of Vascular and Interventional Radiology*. 2007;18(12):1500–1507. [PubMed: 18057284]
13. Manhart MT, Kowarschik M, Fieselmann A, et al. Dynamic iterative reconstruction for interventional 4-D C-arm CT perfusion imaging. *IEEE Trans Med Imaging*. 2013;32(7):1336–1348. [PubMed: 23568497]
14. Neukirchen C, Giordano M, Wiesner S. An iterative method for tomographic x-ray perfusion estimation in a decomposition model-based approach. *Med Phys*. 2010;37(12):6125–6141. [PubMed: 21302769]
15. Ganguly A, Fieselmann A, Marks M, et al. Cerebral CT perfusion using an interventional C-arm imaging system: cerebral blood flow measurements. *AJNR American journal of neuroradiology*. 2011;32(8):1525–1531. [PubMed: 21757522]
16. Fieselmann A, Ganguly A, Deuerling-Zheng Y, et al. Interventional 4-D C-arm CT perfusion imaging using interleaved scanning and partial reconstruction interpolation. *IEEE Trans Med Imaging*. 2012;31(4):892–906. [PubMed: 22203707]
17. Niu K, Yang P, Wu Y, et al. C-Arm Conebeam CT Perfusion Imaging in the Angiographic Suite: A Comparison with Multidetector CT Perfusion Imaging. *American Journal of Neuroradiology*. 2016;37(7):1303–1309. [PubMed: 26892987]
18. Murray T, Rodt T, Lee MJ. Two-Dimensional Perfusion Angiography of the Foot: Technical Considerations and Initial Analysis. *Journal of Endovascular Therapy*. 2016;23(1):58–64. [PubMed: 26668130]
19. Hinrichs JB, Murray T, Akin M, et al. Evaluation of a novel 2D perfusion angiography technique independent of pump injections for assessment of interventional treatment of peripheral vascular disease. *The International Journal of Cardiovascular Imaging*. 2017;33(3):295–301. [PubMed: 27785678]
20. Maschke SK, Renne J, Werncke T, et al. Chronic thromboembolic pulmonary hypertension: Evaluation of 2D-perfusion angiography in patients who undergo balloon pulmonary angioplasty. *European Radiology*. 2017;27(10):4264–4270. [PubMed: 28361177]
21. Maschke SK, Werncke T, Klöckner R, et al. Quantification of perfusion reduction by using 2D-perfusion angiography following transarterial chemoembolization with drug-eluting beads. *Abdominal Radiology*. 2018;43(5):1245–1253. [PubMed: 28840307]
22. Tinelli G, Minelli F, Nigris FD, et al. The potential role of quantitative digital subtraction angiography in evaluating type B chronic aortic dissection during TEVAR: preliminary results. *European Review for Medical and Pharmacological Sciences*. 2018;22(2):516–522. [PubMed: 29424912]
23. Badea CT, Hedlund LW, De Lin M, Mackel JS, Samei E, Johnson GA. Tomographic digital subtraction angiography for lung perfusion estimation in rodents. *Med Phys*. 2007;34(5):1546–1555. [PubMed: 17555236]
24. Markelj P, Tomaževič D, Likar B, Pernuš F. A review of 3D/2D registration methods for image-guided interventions. *Medical Image Analysis*. 2012;16(3):642–661. [PubMed: 20452269]
25. Zeng R, Fessler JA, Balter JM. Respiratory motion estimation from slowly rotating x-ray projections: Theory and simulation. *Medical Physics*. 2005;32(4):984–991. [PubMed: 15895581]
26. Zeng R, Fessler JA, Balter JM. Estimating 3-D Respiratory Motion From Orbiting Views by Tomographic Image Registration. *Medical Imaging, IEEE Transactions on*. 2007;26(2):153–163.
27. Isola AA, Grass M, Niessen WJ. Fully automatic nonrigid registration-based local motion estimation for motion-corrected iterative cardiac CT reconstruction. *Medical Physics*. 2010;37(3):1093–1109. [PubMed: 20384245]
28. Klugmann A, Bier B, Müller K, Maier A, Unberath M. Deformable respiratory motion correction for hepatic rotational angiography. *Computerized medical imaging and graphics : the official journal of the Computerized Medical Imaging Society*. 2018;66:82–89. [PubMed: 29573582]
29. Tang Q, Cammin J, Taguchi K. Four-dimensional projection-based motion estimation and compensation for cardiac x-ray computed tomography The 12th international meeting on fully three-dimensional reconstruction in radiology and nuclear medicine; 7 16–21, 2013; Lake Tahoe, California.

30. Suzuki Y, Fung GSK, Shen Z, et al. Projection-based motion estimation for cardiac functional analysis with high temporal resolution: a proof-of-concept study with digital phantom experiment. *SPIE Medical Imaging*; 2017.
31. Unberath M, Taubmann O, Aichert A, Achenbach S, Maier A. Prior-Free Respiratory Motion Estimation in Rotational Angiography. *IEEE Transactions on Medical Imaging*. 2018;37(9):1999–2009. [PubMed: 29994629]
32. Bier B, Unberath M, Zaech J-N, et al. X-ray-transform Invariant Anatomical Landmark Detection for Pelvic Trauma Surgery. *Medical Image Computing and Computer Assisted Intervention (MICCAI 2018)--International Conference on Medical Image Computing and Computer-Assisted Intervention*. 2018:55–63.
33. Unberath M, Choi J-H, Maier A. Image-based compensation for involuntary motion in weight-bearing C-arm cone-beam CT scanning of the knees *Proc. SPIE 9413, Medical Imaging 2015: Image Processing*, 94130D; 3 18, 2015, 2015; Orlando, FL, U.S.A.
34. Hsieh J Beam hardening In: *In. Computed tomography: principles, design, artifacts, and recent advances* Bellingham, WA: SPIE Optical Engineering Press; 2003:270–280.
35. Erdogan H, Fessler JA. Ordered subsets algorithms for transmission tomography. *Physics in Medicine and Biology*. 1999;44(11):2835–2851. [PubMed: 10588288]
36. Qian C, Wojciech Z, Alejandro S, John Y, Jeffrey HS, Stayman JW. Multiresolution iterative reconstruction in high-resolution extremity cone-beam CT. *Physics in Medicine & Biology*. 2016;61(20):7263–7281. [PubMed: 27694701]
37. Hao D, Stayman JW, Alejandro S, et al. Multi-resolution statistical image reconstruction for mitigation of truncation effects: application to cone-beam CT of the head. *Physics in Medicine & Biology*. 2017;62(2):539–559. [PubMed: 28033118]
38. Segars WP, Mahesh M, Beck TJ, Frey EC, Tsui BMW. Realistic CT simulation using the 4D XCAT phantom. *Medical Physics*. 2008;35(8):3800–3808. [PubMed: 18777939]
39. Segars WP, Tsui BMW, Jing C, Fang-Fang Y, Fung GSK, Samei E. Application of the 4-D XCAT Phantoms in Biomedical Imaging and Beyond. *IEEE Trans Med Imaging*. 2018;37(3):680–692. [PubMed: 28809677]
40. Nakada K, Taguchi K, Fung GSK, Amaya K. Joint estimation of tissue types and linear attenuation coefficients for photon counting CT. *Medical Physics*. 2015;42(9):5329–5341. [PubMed: 26328982]
41. Sauer T, Samei E. Modeling dynamic, nutrient-access-based lesion progression using stochastic processes. *SPIE Medical Imaging*. 2019;10948:1094850.
42. van Aarle W, Palenstijn WJ, De Beenhouwer J, et al. The ASTRA Toolbox: A platform for advanced algorithm development in electron tomography. *Ultramicroscopy*. 2015;157:35–47. [PubMed: 26057688]
43. van Aarle W, Palenstijn WJ, Cant J, et al. Fast and Flexible X-ray Tomography Using the ASTRA Toolbox. *Optics Express*. 2016;24(22):25129–25147. [PubMed: 27828452]
44. Punnoose J, Xu J, Sisniega A, Zbijewski W, Siewerdsen JH. Technical Note: spektr 3.0—A computational tool for x-ray spectrum modeling and analysis. *Medical Physics*. 2016;43(8Part1):4711–4717. [PubMed: 27487888]
45. Lin F, Tzu-Cheng L, Soo Mee K, et al. Comparison Between Pre-Log and Post-Log Statistical Models in Ultra-Low-Dose CT Reconstruction. *IEEE Trans Med Imaging*. 2017;36(3):707–720. [PubMed: 28113926]
46. Isensee F, Petersen J, Klein A, et al. nnU-Net: Self-adapting Framework for U-Net-Based Medical Image Segmentation. In *Bildverarbeitung für die Medizin*. 2019;22 arXiv:1809.10486v1.
47. Vorontsov E, Tang A, Pal C, Kadoury S. Liver lesion segmentation informed by joint liver segmentation. In *2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018)*. 2018:1332–1335. arXiv:1707.07734v3.
48. Yang D, Xu D, Zhou SK, et al. LAutomatic liver segmentation using an adversarial image-to-image network. In *International Conference on Medical Image Computing and Computer-Assisted Intervention*. 2017:507–515. arXiv:1707.08037v1.
49. Huesman RH. A new fast algorithm for the evaluation of regions of interest and statistical uncertainty in computed tomography. *Phys Med Biol*. 1984;29(5):543–552. [PubMed: 6610883]

50. Carson RE. A maximum likelihood method for region-of-interest evaluation in emission tomography. *J Comput Assist Tomogr.* 1986;10(4):654–663. [PubMed: 3488338]
51. Du Y, He B, Frey EC. Iterative reconstruction of combined voxelized images and volumes-of-interest for quantitative SPECT imaging. *Physics in Medicine and Biology* (under review). 2020.
52. Du Y, Frey EC. Iterative reconstruction of combined voxelized images and volumes-of-interest for SPECT imaging. *IEEE Nuclear Science Symposium and Medical Image Conference*; November 1–4, 2006, 2006; San Diego, CA.
53. Xu J, Tsui BMW. Interior and Sparse-View Image Reconstruction Using a Mixed Region and Voxel-Based ML-EM Algorithm. *IEEE Transactions on Nuclear Science.* 2012;59(5):1997–2007.

Figure 1.

The expected workflow to measure soft tissue perfusion using the IPEN algorithm. This paper focuses on Steps 2, 3, and 5 and leaves the other steps for future work. In the pre-operative CT image, the background anatomy is digitally augmented by the lesions for illustration purposes.

Figure 2.

(A–D) The XCAT phantom for Study A with heterogeneous background tissue texture at $t=7$ s with an intra-arterial contrast injection during an interventional procedure, one slice presenting lesion 1 with rim and core sub-sections (A,C) and the other slice showing lesion 2 with anterior and posterior sub-lesions (B,D). The lesion enhancement was homogeneous (A,B) or heterogeneous with the standard deviation of 30% (C,D). The window width and level are 0.21 cm^{-1} and 0.21 cm^{-1} (or 1,000 HU and 0 HU), respectively. (E–H) X-ray projections in the anterior–posterior direction ($j=0^\circ$) at four different time points, depicting contrast-enhanced arteries (E), lesion 1 (arrow) and lesion 2 (curved arrow) (F), and lesion 3 (long arrow) (G). The liver parenchyma was not enhanced. The window width and level are 4 and 4 (dimension less), respectively.

Figure 3.

(A–B) XCAT phantoms for Study D for a pre-TACE scan (A) and one for a post-TACE scan (B) with the heterogeneous background tissue texture and the heterogeneous lesion enhancement with an intra-arterial contrast injection. Lesions of post-TACE phantoms at the baseline ($t=0$ s) had heterogeneously higher voxel values than those of pre-TACE phantoms, simulating the presence of embolic materials with contrast agent. The stochastic offset parameters d_1 for this post-TACE case were 0.056 cm^{-1} or 265 HU for the rim of lesion 1, 0.074 cm^{-1} or 354 HU for the core of lesion 1, and 0.014 cm^{-1} or 67 HU for lesion 3 (arrow). The liver parenchyma was enhanced up to 0.05 cm^{-1} or 238 HU. The window width and level are 0.21 cm^{-1} and 0.24 cm^{-1} (or 1,000 HU and 143 HU), respectively. (C–D) The true TECs for the pre-TACE scan (C) and for the post-TACE scan (D). The stochastic scaling parameters d_2 for this case were 0.449 for the rim of lesion 1, 0.304 for the core of lesion 1, 0.474 for the anterior part of lesion 2, 0.530 for the posterior part of lesion 2, and 0.337 for lesion 3; and the stochastic time delay parameters d_3 were 3.0 s, 1.0 s, 4.8 s, 1.6 s, and 3.6 s, respectively. Ant=anterior, Post=posterior.

Figure 4.

The true and the mean estimated TECs over 20 phantoms at four different noise/dose levels with homogeneous lesion enhancement and no 3×3 -pixel averaging. The standard deviations were very small, thus, not presented. Ant=anterior, Post=posterior.

Figure 5.

The true and estimated TECs at four different noise/dose levels with homogeneous lesion enhancement and with 3×3 -pixel averaging. Ant=anterior, Post=posterior.

Figure 6.

The biases in the estimated TECs plotted over (A) relative volume (r_{vol}) and (B) Sorensen–Dice Coefficient (SDC) due to inaccurate ROI contours used in IPEN estimation. Error bars are the standard deviations of biases over 10 scans, which were very small ($<0.0002 \text{ cm}^{-1}$). Presented on the right are the true and two created ROIs for lesion 3.

Figure 7.

The true and the mean of the estimated TECs, with the smallest ROIs (A), the accurate ROIs (B), and the largest ROIs (C) in Study B. The standard deviations were very small, thus, not presented.

Figure 8.

(A-C) The results of Study C with setting C1 (A), setting C2 (B), and setting C3 (C). Error bars are the standard deviations over 10 scans. (D) The polar angle θ and the view angle φ . A=Anterior, P=Posterior, R=Right, L=Left, S=Superior, and I=Inferior.

Figure 9.

Scatter plots of the estimated perfusion index values against the true index values for time-to-peak (A) and max-slope (B). The linear correlation coefficient was 0.859 ($P<0.0001$; regression line, $y=0.97x+0.02$) for the time-to-peak and 0.998 ($P<0.0001$; regression line, $y=1.00x+0.00$) for the max-slope.

Table 1.

The mean and the standard deviation of RMSD values for 16 settings assessed in Study A.

n_0 (photons/pixel)	<i>Homogeneous</i>		<i>Heterogeneous</i>	
	Without 3×3-pixel averaging	With 3×3-pixel averaging	Without 3×3-pixel averaging	With 3×3-pixel averaging
1×10^3	0.0412±0.0010	0.0093±0.0003	0.0414±0.0013	0.0096±0.0005
2×10^3	0.0220±0.0003	0.0051±0.0002	0.0224±0.0008	0.0054±0.0005
5×10^3	0.0062±0.0002	0.0017±0.0001	0.0066±0.0005	0.0023±0.0004
1×10^4	0.0027±0.0001	0.0011±0.0001	0.0032±0.0005	0.0018±0.0004

Table 2.

The mean and the standard deviation of the absolute differences in RMSD values between a pair of settings relative to the mean RMSD of the first setting. The values inside parentheses are *P* values.

n_0 (photons/pixel)	<i>Homogeneous vs heterogeneous</i>		Without vs with 3×3-pixel averaging	
	Without 3×3-pixel averaging	With 3×3-pixel averaging	<i>Homogeneous</i>	<i>Heterogeneous</i>
1×10^3	0.6±1.4% (<i>P</i> =0.0622)	3.3±5.2% (<i>P</i> =0.0109)	77.4±2.2% (<i>P</i> <0.0001)	76.9±2.4% (<i>P</i> <0.0001)
2×10^3	1.5±3.6% (<i>P</i> =0.0768)	7.7±11.2% (<i>P</i> =0.0059)	77.1±1.1% (<i>P</i> <0.0001)	75.7±1.7% (<i>P</i> <0.0001)
5×10^3	6.4±8.3% (<i>P</i> =0.0028)	35.7±22.2% (<i>P</i> <0.0001)	72.8±2.5% (<i>P</i> <0.0001)	65.3±4.3% (<i>P</i> <0.0001)
1×10^4	17.7±17.0% (<i>P</i> =0.0002)	69.8±37.9% (<i>P</i> <0.0001)	61.4±6.5% (<i>P</i> <0.0001)	44.3±9.9% (<i>P</i> <0.0001)