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Perfusion measurements by micro-CT using Prior Image Constrained Compressed Sensing (PICCS): Initial Phantom Results

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Abstract

Micro-CT scanning has become an accepted standard for anatomical imaging in small animal disease and genome mutation models. Concurrently, perfusion imaging via tracking contrast dynamics after injection of an iodinated contrast agent is a well established tool on clinical CT scanners. However, perfusion imaging is not yet commercially available on the micro-CT platform. Recent hardware developments in micro-CT scanners enable continuous imaging of a given volume through the use of a slip-ring gantry. Now that dynamic CT imaging is feasible data may be acquired to measure tissue perfusion using a micro-CT scanner (CT Imaging, Erlangen, Germany). However, rapid imaging using micro-CT scanners leads to high image noise in individual time frames. Using the standard filtered backprojection (FBP) image reconstruction images are prohibitively noisy for calculation of voxel-by-voxel perfusion maps. Here we apply Prior Image Constrained Compressed Sensing (PICCS) to reconstruct images with significantly lower noise variance. In perfusion phantom experiments performed on a micro-CT scanner the PICCS reconstruction enabled a reduction to 1/16 of the noise variance of standard FBP reconstruction, without compromising the spatial or temporal resolution. This enables a significant increase in dose efficiency and thus significantly less exposure time is needed to acquire images amenable to perfusion processing. This reduction in required irradiation time enables voxel-by-voxel perfusion maps to be generated on micro-CT scanners. Sample perfusion maps using a deconvolution based perfusion analysis are included to demonstrate the improvement in image quality using the PICCS algorithm.

Keywords

micro-CT; perfusion; dynamic; dose

1. INTRODUCTION

Small animal imaging offers a non-invasive means to gain information on small animal disease models, genetic modifications in small animal models and the use of drug or radiation delivery in small animals [1–14]. Small animal imaging enables studies of the phenotype manifestations of genome modifications. Micro-CT (micro-Computed Tomography) has become a standard

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for high spatial resolution anatomical imaging of small animals. The high spatial resolution, reproducibility, uniformity and linearity of micro-CT imaging make it ideal for several quantitative applications in small animal imaging [10,15]. Many of the first applications of micro-CT involved the study of bones and measurement of quantitative changes in different disease models [5,7,12]. The standard micro-CT scanners currently available utilize micro-focus x-ray tubes and flat panel imagers. The typical micro-CT volumetric acquisition on such a system takes several minutes in order to acquire high quality, relatively low noise images. Therefore, the commercially available micro-CT scanners do not enable dynamic contrast-enhanced acquisitions in the standard mode.

In addition to the anatomical imaging of small animals there is significant interest in making physiological measurements, and combination systems which enable molecular imaging on the same platform as the anatomical imaging with micro-CT have been developed [16–19]. One well accepted means of making physiological measurements on clinical CT scanners is the now standard generation of perfusion parametric maps including cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) [20–28]. In other cases such as in the case of tumor perfusion the measurement of the tumor membrane permeability can provide useful information [29–33]. Small animal perfusion measurements have been made in rat models on clinical CT scanners where angiogenesis was measured with CT perfusion and confirmed by histology [34–36]. While clinical CT has high temporal resolution (i.e. ~300 ms/revolution) it does not offer sufficient spatial resolution to properly visualize smaller organs and tumors in standard mouse models. Thus, there is a desire to perform perfusion measurements on high spatial resolution micro-CT scanners, to make perfusion measurements on mice tumors for instance. To the best of the authors' knowledge, there are currently no micro-CT perfusion packages offered by micro-CT vendors.

The Tomoscope Duo micro-CT scanner (CT Imaging GmbH, Erlangen, Germany) utilizes a slip-ring gantry to enable dynamic CT acquisitions. This system utilizes a micro-focus tube with a focal spot size of 50 micrometers to maintain high isotropic resolution. In order to follow dynamic processes CT images must be acquired on the order of seconds rather than minutes. However, as the exposure time is reduced the noise in the CT images becomes substantial. As is demonstrated in this manuscript when standard filtered backprojection image reconstruction is utilized the noise in the individual time frames makes perfusion analysis difficult. The perfusion values may be measured in large ROIs within the FBP images, but parametric perfusion maps generated on a voxel by voxel basis are significantly degraded by quantum noise. Thus, in order to generate practically acceptable perfusion maps an alternative reconstruction method may be required. In this work, a new image reconstruction algorithm, Prior Image Constrained Compressed Sensing (PICCS), [37,38] is used to significantly reduce the noise in the reconstructed micro-CT images and thus enables perfusion measurement. The PICCS reconstruction algorithm is an extension of the Compressed Sensing (CS) framework [39–45], by incorporating a low noise prior image into the objective function of the iterative algorithm. As demonstrated in previous publications, the PICCS algorithm enables improved reconstruction compared with CS alone as the noise properties are to a large extent inherited from the prior image. The PICCS algorithm has been applied to a variety of applications in diagnostic CT imaging and flat panel cone-beam CT imaging[38,46–49]. To our knowledge the PICCS algorithm has not yet been applied to micro-CT image reconstruction. Specific implementation details for micro-CT perfusion are included here, where three separate choices for the prior image are compared. As demonstrated here high resolution parametric perfusion maps may be generated with practically acceptable noise levels using the PICCS algorithm. Thus, the phantom measurements performed here demonstrate that the PICCS algorithm enables perfusion measurements on conventional micro-CT scanners.

2. METHODS AND MATERIALS

2.1 Experimental Acquisition: Phantom and acquisition parameters

Phantom—In this study, an experimental phantom was used to simulate small animal perfusion measurements. The phantom was constructed at the University of Erlangen-Nuremberg [50].

The phantom utilizes liquid filled tubes as the simulated arteries and veins, and a porous medium is used to simulate the tissue beds. The phantom is driven by a peristaltic pump and contrast is injected into the circulation system in much the same manner that intravenous injections are used for clinical perfusion exams. The phantom supports a re-circulation mode, but in the studies presented here the re-circulation mode was not used. Reconstructed images of the phantom from two different time points are shown in Figure 1, where several regions of interest (ROIs) are defined and will be referenced below.

System Parameters—The experimental acquisitions were conducted using a TomoScope Duo micro-CT scanner (CT Imaging GmbH, Erlangen, Germany). The system is slip-ring based to support dynamic CT scanning. There are three modes of image acquisition currently supported on the TomoScope system: standard quality, high quality and high speed. The TomoScope system is a dual-source micro-CT scanner but in order to keep this protocol straightforward only data from a single source has been used in the results presented here. The incorporation of the second source could offer an improvement of approximately a factor of two in temporal resolution. In this study, the high speed mode was used. In this mode the system typically reconstructs axial images on a 512×512 grid with a pixel linear dimension $80 \mu\text{m}$. In the high speed mode 100 total projection view angles are used in each image reconstruction. The x-ray parameters used in these reconstructions were 40 kVp, 0.8 mA and 40 ms per view. In this high speed mode the gantry rotates at a rate of $90^\circ/\text{sec}$. Reconstructions were performed in 1 second intervals, with full scan data from a 360° range.

2.2 Reconstruction

The standard image reconstruction method used on the TomoScope Duo micro-CT scanner is the filtered backprojection algorithm (FBP) [51–53]. This is also the standard method used to reconstruct clinical CT perfusion exams. Therefore, the FBP reconstruction will serve as the standard of comparison with the image reconstruction methods presented here. Given the speed of the FBP reconstruction it has served as the de facto standard for CT image reconstruction. However, the standard FBP algorithm has limited means to suppress noise in the reconstructed images. Thus, in the low dose scanning protocol used in dynamic micro-CT, images reconstructed with the FBP algorithm may be quite noisy. This noise in the individual time frame images makes it difficult to calculate the parametric perfusion maps as the contrast pass curve for each pixel within the image may be severely contaminated by noise. Given hardware limitations from the x-ray flux available with micro focus tubes it is not possible for micro-CT scanners to deliver an arbitrarily high dose per view during a dynamic acquisition. In this work, we will use a new image reconstruction algorithm, Prior Image Constrained Compressed Sensing (PICCS), to significantly reduce the image noise variance and improve dose efficiency.

The PICCS algorithm has been applied to several different clinical scenarios in x-ray CT including: low dose myocardial perfusion, temporal resolution improvement in cardiac CT angiography, 4D CBCT (cone-beam CT) for guiding lung cancer treatment, measuring cardiac function on interventional C-arm systems and low dose monitoring of image guided procedures [38,46–49]. The PICCS algorithm was developed to overcome some of the shortcomings of standard compressed sensing reconstruction, such as the presence of patchy image artifacts in the reconstructed images even when 100 projection view angles are used [54]. The inclusion

of a prior image into the objective function enables the PICCS algorithm to inherit the high SNR property of a high quality prior image. The objective function for the PICCS algorithm is given in Eq. 1:

$$\min \alpha \left\| \psi_1(\mu - \mu_p) \right\|_1 + (1 - \alpha) \left\| \psi_2 \mu \right\|_1 \text{ s.t. } \mathbf{A}\mu = \mathbf{y} \quad (1)$$

where μ is the image to be reconstructed, μ_p is the prior image, ψ_1 and ψ_2 are sparsifying transforms, $\mathbf{A}$ is the system matrix, $\mathbf{y}$ is the projection data, and α is the relative weighting between the two terms in the objective function. The implementation of the PICCS algorithm is performed with in-house software and has been published previously [38,46,49]. The minimization is performed here with an alternating implementation procedure where several steps are taken in a steepest decent minimization of the objective function and the measured data is enforced on the solution using the SART algorithm[55]. In this work both of the sparsifying transforms were the gradient operator

$\psi_1(\mu) = \psi_2(\mu) = \nabla(\mu) = \sqrt{(\mu_{m+1,n} - \mu_{m,n})^2 + (\mu_{m,n+1} - \mu_{m,n})^2}$. All results shown here correspond to 10 SART iterations. The value for α was chosen empirically as 0.67 for all of the results shown here, but the selection of the parameter is not very sensitive and comparable results are achievable within the range from 0.6–0.8. Each application of the PICCS algorithm requires a prior image μ_p , which is similar to the image to be reconstructed. In this paper three possible selections of the prior image are studied.

2.3 Generation of the Prior Image μ_p

Option 1: Full Average Prior Image ($\mu_p = \bar{\mu}$)

The first choice for the prior image is the average image over all of the acquired time frames in the series, where each time frame is reconstructed using the standard FBP algorithm.

Option 2: Running Average Prior Image ($\mu_p = \bar{\mu}_N$)

A second choice for the prior image which has increased image noise, but which contains some information about the temporal dynamics of the given time frame is a running average, where the prior is a centered average of the nearest N time frames.

Option 3: Vessel Selective Prior Image ($\mu_p = \bar{\mu}_{VS}$)

A third choice of prior image which has been designed specifically for this application is a vessel selective prior where the image pixels with high contrast vascular structures are treated differently than the other pixels in the image. Since the vessels may be very small (i.e. a high spatial resolution task) and their density values may vary rapidly (i.e. a high temporal resolution task) they may be particularly challenging to reconstruct accurately when a full average prior image is used. When the running average prior is used the vessels may be reconstructed more accurately but at the cost of a reduced signal to noise ratio in the tissue bed, where the perfusion measurement parameters are to be estimated. Therefore, we propose a vessel selective prior image where the vascular pixels are reconstructed using the running average prior $\bar{\mu}_N$ and the tissue pixels are reconstructed using the full average prior $\bar{\mu}$. In this manner the desired characteristics of the full average and the running average prior are combined into a single prior image that we term the vessel selective prior. The vessel selective prior image incorporates both a spatial weighting and a temporal weighting in order to isolate the pixels within the vessels at the time of contrast enhancement. The input to compute the vessel selective prior is the time sequence of FBP images. To illustrate the method, a two dimensional image sequence

is used in Figure 2, but the extension to the fully four dimensional case (three spatial dimensions and one temporal dimension) is straightforward. The first several time frames of the series are typically acquired before contrast has arrived. These frames serve as a mask image in order to subtract the static background anatomy. After the mask has been subtracted from the images we refer to the image set as the difference FBP images or $dFBP(x_1, x_2, t)$ where x_1 and x_2 are the spatial variables and t is the temporal variable. An assumption in the vessel selection is that pixel with the highest value in $dFBP(x_1, x_2, t)$ corresponds to the maximum enhancement in the arterial function, which occurs at time $t_{\max}$. In order to define a spatial map a weighted temporal maximum intensity projection (MIP) is taken by applying a smooth weight centered on the time point of maximal enhancement, i.e.,

$$dFBPMax(x_1, x_2) = \max_t(dFBP(x_1, x_2, t) \cdot \frac{1}{\sqrt{2\pi}\sigma^2} e^{\frac{-(t-t_{\max})^2}{2\sigma^2}})$$

In this work the value of σ was 5 seconds. After the $dFBPMax(x_1, x_2)$ image is calculated, the following standard image processing steps are performed in order to create the spatial vessel mask (Figure 2). Note that these operations only need to act on $dFBPMax(x_1, x_2)$, which is a single image. To reduce the noise the image is first smoothed by convolution with a two dimensional Gaussian function of width of 5 image pixels. Then a threshold procedure was performed to isolate the vascular pixels based on their attenuation. As can be seen from Figure 2 the relative signal to background ratio in the $dFBPMax(x_1, x_2)$ image is high. Therefore, the threshold value may be selected from a wide range of values, and quality of the spatial mask will not be highly sensitive to the threshold value chosen. Finally the mask image is dilated using a circular function of width 3 pixels. The aim is to have a mask that is slightly larger than the vessel footprint. The final step is to convolve the binary mask with a Gaussian function of width 5 image pixels such that the transition between the vascular and non-vascular regions is smooth. The spatial mask is referred to as $\Phi(x_1, x_2)$.

Additionally a temporal mask is defined so that in the beginning and end of the image sequence the vascular pixels are treated in the same manner as the tissue pixels. This is because the vascular pixels do not vary rapidly before the addition of contrast or after the contrast has flowed out. To calculate the temporal weighting function the mean vascular enhancement is calculated as $\chi(t) = dFBP(x_1, x_2, t) \cdot \Phi(x_1, x_2)$. A sample plot of $\chi(t)$ is given in Figure 3 (A). The mean vascular enhancement is the input to calculate a smooth temporal weighting function. The smooth temporal weighting, $\Theta(t)$, was chosen here to be the sum of two Fermi functions with opposite signs (Figure 3(B)). The pixels within the vessel mask are weighted by one during enhancement and zero before and after enhancement, with a smooth transition between phases. Note, that other smooth temporal weights would also suffice, as would other methods of accurately of estimating the vessel mask. After calculation of the spatial weighting and the temporal weighting the final prior image may be calculated for each time frame:

$$\bar{\mu}_{VS}(x_1, x_2, t) = \Theta(t) \{ \Phi(x_1, x_2) \cdot \bar{\mu}_N(x_1, x_2, t) + (1 - \Phi(x_1, x_2)) \cdot \bar{\mu}(x_1, x_2) \} + (1 - \Theta(t)) \cdot \bar{\mu}(x_1, x_2), \quad (2)$$

where, each of the components of $\bar{\mu}_{VS}(x_1, x_2, t)$ have been defined above. Note that both the spatial and temporal weighting range from 0 to 1. It is helpful to examine the limiting cases of the expression above, where we suppress the parameters for brevity. For instance consider the case where $\Theta(t) = 0$ which corresponds to the beginning and end of the acquisition when there are no rapid changes in the vessels. In this case $\bar{\mu}_{VS} = \bar{\mu}$, ie. the vessel selective prior is equal to the full average as there are no vessels present. Another limiting case is when $\Theta(t) = 1$, which corresponds to the case when the vessels are highly enhanced. In this case we can see that the vessel selective image is $\bar{\mu}_{VS} = \Phi \cdot \bar{\mu}_N + (1 - \Phi) \cdot \bar{\mu}$, where the vessel values are given by the

running mean $\bar{\mu}_N$ of the nearest N frames and the values in the tissue, bone and air regions in the image are given by the full average $\bar{\mu}$. After images are reconstructed for each time frame they are input directly to the perfusion processing software without any post processing.

2.4 Perfusion Parameter Calculation

Depending upon the anatomical site (e.g. brain, heart, kidneys or a tumor), different physiological modeling is appropriate. Some tissue is well modeled as a single compartment, while other sites a membrane through which contrast may leak out of the ‘tissue compartment’ during data acquisition. Additionally, for each given anatomical site there are multiple approaches to calculate the perfusion parameters depending upon the assumptions made about the acquisition and the injection rate. The perfusion maps provided here were generated using our in-house software. We consider the case of brain perfusion where the standard parametric maps are those of cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT). For a review of the deconvolution approach used here refer to the summary given by Lee [56] and references therein. The same terminology will be used here. The measured time density curve (TDC) in the artery and vein will be referred to as $C_A(t)$ and $C_V(t)$ respectively, and the measured TDC in the tissue will be referred to as $Q(t)$. Given these measured TDCs, and assuming a linear systems model with a constant flow rate F , the aim of the deconvolution approach is solve for the flow and the impulse response function $R(t)$

$$Q(t)=[C_A(t) \otimes F R(t)] \quad (3)$$

where $\otimes$ denotes the convolution operation. As demonstrated by Ostergaard the deconvolution approach provides the best results in terms of noise suppression without biasing the perfusion measurements[57,58]. In this work the threshold value of 20% of the maximal value in the diagonal matrix. In order to enforce the physiological constraint that the residual function should be smooth additional constraints may also be added to the deconvolution procedure [59]. In this work we used a standard Lagrange multiplier where the aim of the deconvolution procedure is to minimized the sum of a data matching norm and a smoothness norm as given here

$$\min\left\{\|Q - \tilde{Q}\|^2 + \lambda \left\|\frac{d^2 \tilde{R}}{dt^2}\right\|^2\right\} \quad (4)$$

where the second derivative is used as the smoothness norm, $\tilde{Q}$ and $\tilde{R}$ are the estimates signals after the deconvolution procedure. A universal value for the Lagrange multiplier was used for all image values which was selected using the standard L-plot which is generated by plotting the smoothness norm as a function of the residual norm on a log-log scale [59]. In this work the value of 250 was used for all cases, as it provided adequate suppression of spurious fluctuations while not overly smoothing the generated impulse response function. Note that the value of λ is sensitive to the scanning interval and the length of the vectors to be deconvolved, but these were held constant for the comparisons made here. A final implementation detail is that in reality a non-causal relationship may occur between the arterial input function and the tissue function, for instance when the input is chosen from a diseased region. Different methods have been proposed in the literature to address this issue including delay correction [60] and block circulant SVD [61]. Kudo et. al. found superior results using the block circulant SVD[62], so this method was used here.

Thus, to summarize the deconvolution procedure used here incorporates noise suppression (i.e. the singular value deconvolution SVD), incorporates a smoothness constraint (i.e. Lagrange

multiplier) and is robust to signal delay (block circular SVD). In the deconvolution procedure used here there is no correction for dispersion of the arterial input function from the time of measurement till it reaches the tissue bed. To the best of the author's knowledge such high order dispersion corrections are also not yet a feature in the deconvolution packages offered by commercial vendors. As mentioned when measuring perfusion in other anatomical sites different modeling may be suitable such as Patlak analysis [63,64] for myocardial perfusion or tumor perfusion, where the permeability of the 'tissue compartment' is also of concern. The case of brain perfusion metrics is given here as an example application but the PICCS reconstruction algorithm is independent of the anatomical site.

3. RESULTS

3.1 Image Quality Evaluation and Comparison

3.1.1 Qualitative Assessment of the Reconstructed Images—Images were reconstructed using the standard FBP algorithm as well as the PICCS algorithm with three choices for the prior image $\mu_p = \bar{\mu}$ (the full average prior), $\mu_p = \bar{\mu}_N$ (the running or moving average prior) and $\mu_p = \bar{\mu}_{VS}$ (the vessel selective prior). Reconstructed images are shown at two sample time frames in Figure 4 to compare the image quality using each algorithm. In each case the preferred reconstructions are provided by the $\bar{\mu}_{VS}$ prior as the vessels are clearly delineated and the perfusion signal is reproduced with significantly lower image noise than the FBP counterpart. In order to visualize just the injected contrast, a mask subtraction is performed for each case where an average of the first five images was used as the mask for background subtraction. This is the standard processing before the parametric perfusion maps are calculated. The images to be compared are shown in Figure 5 where again all of the PICCS results show a reduction in the noise compared with the FBP images and the full average prior and vessel selective prior show the most improvement in noise characteristics without losing the actual enhanced areas.

3.1.2 Comparison of Temporal Dynamics—The calculation of perfusion parameters requires that the image reconstruction algorithm provides an accurate assessment of the temporal dynamics within the object from frame to frame. Unfortunately, for these phantom measurements there is no gold standard available. The clinical CT scanners have superior temporal resolution to the micro-CT scanner (less than 300 ms per rotation), but unfortunately the spatial resolution of these exams is insufficient to resolve some of the small structures within this phantom. On the other hand high quality (i.e. low noise) exams are possible on the micro-CT scanner, but the scanning times can be on the order of minutes and are not suitable for dynamic acquisitions. The FBP reconstructions should capture the temporal dynamics but are contaminated by a significant amount of noise in the reconstructed images. However, when tracking the attenuation in large regions of interest (ROIs) the effect of the quantum noise is largely removed by the averaging of many pixels. Thus, the values of the FBP images in large ROIs will serve as a standard for comparison of the accuracy of the reconstruction of the temporal dynamics within the acquisition. In Figure 1 we demonstrate several ROIs which will be used to observe the change in reconstructed attenuation as a function of time. In Figure 1 A the tissue ROIs are shown (ROI₁– ROI₃) along with a background ROI, ROI₄ which is not enhanced by contrast and will be used to make noise measurements. Figure 1 B shows the vascular ROIs (ROI₅– ROI₆) used to assess the ability of PICCS to capture rapid dynamic changes. In all plots a median filter of length three was used. Figure 6 and Figure 7 demonstrate the ability of the PICCS algorithm to preserve the contrast dynamics within the arteries and within the 'tissue bed', respectively. A small underestimation of the arterial input function (AIF) is observed in the PICCS reconstructions (Figure 6). This underestimation is not of a significant drawback for the method as the arterial input function may be taken from the FBP reconstructions and will not be contaminated by noise. This is because the AIF is an average

over several pixels and the signal level is quite high in the opacified arteries. The more important task for the perfusion measurements is the ability to reconstruct the signal values with the ‘tissue bed’. In Figure 7 (a) the agreement between the average values within a tissue ROI is demonstrated. The reconstruction of contrast dynamics for single pixels in the image, i.e. very small ROIs, is also plotted for a randomly chosen single pixels within ROI₂ (Figure 7 (b)). These plots are also important to gain an appreciation for the noise within each pixel’s time density curve. This is important as the individual pixel curves are used for the calculation of parametric perfusion maps. The quantum and streaking noise present in the FBP reconstruction images induce significant fluctuations when the values are examined on a single pixel basis. These fluctuations are not physically realistic as the tissue enhancement curve in the phantom should be smoothly varying. In contrast, the PICCS reconstructions display the expected behavior on a pixel by pixel basis.

3.1.3 Comparison of Image Noise—The image noise was assessed on a frame by frame basis using the standard deviation of the image values in a background region of interest (Figure 1 (A)-ROI₄). The image noise was plotted as a function of time frame and the average noise over all time frames was compared to assess the potential dose savings of the PICCS algorithm. As the PICCS reconstruction with the running mean as the prior used only seven frames averaging it is not surprising that the noise was higher than the other PICCS reconstructions. On average the PICCS algorithm with the average prior or the vessel selective prior had a standard deviation of 0.25 times the standard deviation of the FBP, as measured in a tissue ROI. Thus, the variance in the noise is 16 times lower for the PICCS reconstruction technique than the FBP reconstruction. Typically, the delivered dose is proportional to the noise variance in the image. However, we do note that streaking artifacts due to low sampling would also increase this noise measurement, in addition to the quantum noise. If the view angle sampling changes or the delivered exposure changes the relative contribution of quantum and streaking noise may change.

3.1.4 Comparison of Spatial Resolution—Typically, there is a trade-off in image reconstruction between spatial resolution and image noise. For instance in standard FBP reconstruction manipulating the filter kernel enables one to reduce the image noise at the cost of reduced spatial resolution. Given a reduction in image noise for a given reconstruction technique it is important to demonstrate that spatial resolution has not been compromised to achieve the noise reduction. For non-linear reconstruction techniques such as the Compressed Sensing and Prior Image Compressed Sensing algorithms it is important to make all image assessments in the presence of realistic anatomical background, as sparse piecewise constant phantoms such as a wire phantom are ideally suited for CS reconstruction [54]. Additionally, for techniques which use frame averaging the stationary tissue will inherit the spatial resolution of the individual time frames. The most challenging task is to preserve the spatial resolution in the dynamically changing portions of the image such as the vessels. The perfusion phantom includes narrow vessels, of diameter 0.4mm, which may be used to assess the spatial resolution. At the peak vascular enhancement the upper-most vessel is used as a surrogate for the point spread function (PSF). This method does not provide an absolute measure of spatial resolution, but it does provide a relative metric for comparing the PICCS results with the FBP results. Two orthogonal profiles through the vessel were averaged and a Gaussian fit was performed for both the PICCS reconstructions and FBP reconstructions. The surrogate PSF and the corresponding plots are given in Figure 9. The fit to the line profiles yielded a measurement of the full width at half maximum value of 5.53 pixels for the FBP reconstruction and 5.60 pixels for the PICCS reconstruction. Note, this is not a true MTF measurement and the conclusions are only valid for objects of this diameter and larger. As expected the PICCS algorithm does not significantly degrade the spatial resolution.

3.2 Parametric Perfusion Maps

Parametric perfusion maps of the CBF, MTT and CBV are presented to compare the standard FBP with the PICCS results. In all cases the same window and level parameters are used for these comparative maps.

The noise variance in the FBP parametric maps is very high. In practice one method for reducing the noise variance in the perfusion maps is to perform a low-pass filter [56]. This filter will reduce the image noise at the cost of reduced spatial resolution. A Gaussian filter was applied to the FBP reconstructions in order to most closely match the noise variance in the PICCS results. Thus, the perfusion maps were convolved with a Gaussian filter with a sigma of 5 image pixels to the FBP in order to generate the 'Low-pass FBP' results that are also given for comparison with the FBP and PICCS results. In Figures 10–12 parametric perfusion maps are compared between FBP, low-pass FBP and PICCS. The parameters of Cerebral Blood Flow (CBF-Figure 10), Cerebral Blood Volume (CBV-Figure 11) and Mean Transit Time (MTT-Figure 12) are each compared. In all cases the perfusion processing and image display is identical as described above. In the case of CBV and MTT there is so much noise in the initial FBP data that it is difficult to appreciate any pattern in the parametric maps.

The PICCS results show improved visualization of each of the perfusion parameters as the regions of high CBF, CBV and MTT are continuous whereas in the low-pass FBP images the elevated areas in each perfusion map are disjointed and contain unphysical sporadic changes in parametric values.

4. SUMMARY AND OUTLOOK

The PICCS algorithm was utilized to reconstruct dynamic data from contrast-enhanced perfusion acquisitions on a micro-CT scanner. As was demonstrated in this paper, perfusion analysis is difficult with standard micro-CT scanners when the standard filtered backprojection image reconstruction. This is due to a large contribution from the noise in each individual time frame. Perfusion values may be measured in large ROIs within the noisy FBP images, but parametric perfusion maps generated on a voxel by voxel basis are significantly degraded by quantum noise. The PICCS reconstruction algorithm was used here as an enhancing technique to standard FBP reconstruction. Namely, the FBP method is first used to reconstruct high noise individual time frames and a prior image is generated using the FBP images. The PICCS algorithm is then used to reconstruct each individual time frame for the purpose of noise reduction. The algorithm enabled a reduction in the variance of the image noise in phantom measurements of a factor of 16. Concurrently, measurements were made to ensure that the noise reduction was achieved without degradation of the spatial resolution or temporal resolution. This leads to a gain of a factor of 16 in dose efficiency. As demonstrated here high-resolution parametric perfusion maps may be generated with practically acceptable noise levels using the PICCS algorithm, whereas the noise and streak content in the FBP images yielded them un-amenable for perfusion processing. Thus, the phantom measurements performed here demonstrate that the PICCS algorithm enables perfusion measurements on currently available micro-CT scanners. Experimental studies using a mouse model on this system are ongoing and will be reported in subsequent publications. The methods presented here are designed for measurement of cerebral perfusion, kidney perfusion or tumor perfusion. The subject of measuring cardiac perfusion is a separate entity that requires higher temporal resolution. Highly undersampled acquisition schemes have been proposed including distributed x-ray sources (e.g. carbon nanotubes [65]) and multiple injection protocols [66]. The PICCS algorithm has also been applied to highly undersampled acquisitions but the subject of myocardial perfusion measurements is beyond the scope of the present work.

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Figure 1.
Example filtered backprojection reconstruction shown at the peak tissue time frame (A) and the peak arterial time frame (B). Six regions of interest (ROIs) are labeled. These ROIs will be used to compare average signals between the FBP and PICCS reconstructions.

Figure 2. Demonstration of the generation of the spatial weighting, or the smooth vessel mask $\Phi(x_1, x_2)$. The steps for generating the smooth vessel mask are described in detail in the text.

Figure 3. Plot of the average temporal dynamics of the pixels within the vessel mask (A), and the smooth temporal weighting function defined for the vascular pixels (B).

Figure 4. Comparison of images reconstructed with the FBP algorithm and the PICCS algorithm with three choices of the prior image. Reconstructions are shown for the peak arterial time frame (A) and the peak tissue time frame (B).

Figure 5. Comparison of mask subtracted images reconstructed with the FBP algorithm and the PICCS algorithm with three choices of the prior image. Reconstructions are shown for the peak arterial time frame (A) and the peak tissue time frame (B).

Figure 6.
The fidelity of the PICCS algorithm in recovering the temporal dynamics within small arteries is shown for ROI₅ (A) and ROI₆ (B). In (A) and (B) there is a slight underestimate by each of the PICCS results but the vessel selective prior comes closest to the FBP results and in each case the signal shape is preserved.

Figure 7. The fidelity of the PICCS algorithm in recovering the temporal dynamics of large ROIs within the 'tissue bed' is given here for ROI₁ (A) and ROI₂ (B). All PICCS results well track the FBP results for these ROI measurements within the tissue bed. In this case many of the points for different parameter choices have the same value and thus not all points are visible as they are overlapping in the plot. This is expected for the selective prior points to lie exactly over the Full Avg. prior points as the pixels in the tissue region are processed with the full prior.

Figure 8.

Comparison of the standard deviation of image noise within a background ROI. There are three separate noise levels: the FBP (dark line), the PICCS with moving average (green circles) and all other PICCS reconstructions as tissue ROIs are treated the same in the vessel selective and full average cases.

Figure 9. A comparison of the spatial resolution measurements within a small dynamic vessel. The point spread function surrogate is shown in the upper left portion (A) for the FBP reconstruction and (B) for the PICCS reconstruction with a vessel selective prior. The averaged line profile and its Gaussian fit are plotted for both cases as well.

Figure 10.
Comparison of the CBF maps for the FBP (A), low-pass FBP (B) and PICCS reconstructions with a vessel selective prior (C).

Figure 11.
Comparison of the CBV maps for the FBP (A), low-pass FBP (B) and PICCS reconstructions with a vessel selective prior (C).

Figure 12. Comparison of the MTT maps for the FBP (A), low-pass FBP (B) and PICCS reconstructions with a vessel selective prior (C).