Supplementary Material

Regressions of Trends in Reconstructed Voxel Intensity

All regressions were performed by directly comparing the results for the EM to the FBP by incorporating a logical indicator variable for the EM, \( \delta_{EM} \), into the regressions. The full equation of the quadratic model fit is:
\[
Y = \beta_{0,FBP} + \beta_{1,FBP}I + \delta_{EM}(\beta_{0,EM} + \beta_{1,EM}t + \beta_{2,EM}t^2) + \varepsilon
\]
where the \( \varepsilon \) vector is the independent, identically distributed Gaussian stochastic error term, the I vector indicates original intensity, the Y vector reflects the bias or variance and the \( \beta \) vector reflects the fitted non-linear parameters. The model was fit in this way because \( \beta_{0,EM} \) and \( \beta_{1,EM} \) reflect the change in the model attributable to the EM algorithm. The quadratic term was not included for the FBP because, when fit, its coefficient was not significantly different from zero (p>0.4).

Reconstruction Algorithms

The Radon projection, \( m(t, \theta) \), for angles from 0 to 179 degrees of this noisy image was defined by the line integral over the line \( l(t, \theta) \) for \( t = x\cos \theta + y\sin \theta \) for the image, \( I(x,y) \):
\[
m(t, \theta) = \int l(t, \theta) \cdot I(x,y) \, ds
\]

The filtered back projection (FBP) reconstruction calculates the reconstructed image, \( I(x, y) \), based on the convolution, *, of the projection with the ramp filter, \( g(t) \), using the formula below. In this case, \( \Delta \theta \) is 1 because the angles of projections are in integer steps.

\[
I(x, y) = \sum_{\theta=0}^{179} m(t, \theta) \ast g(t) \Delta \theta
\]

In the EM reconstruction, the initial reconstructed image had uniform intensity 1. The following formula was used for the iterative updates of the EM, where the A matrix was calculated as the point spread functions of individual voxels of intensity 1 in each position of the image. The superscript indicates the iteration index. The sums with two indices indicate double sums.

\[
I(x, y)^{(n+1)} = \frac{\sum_{t, \theta} \left( \frac{m(t, \theta)A(x,y,t,\theta)}{\sum_{x,y} A(x,y,t,\theta)I(x,y)^{(n)}} \right)}{\sum_{t, \theta} A(x,y,t,\theta)}
\]

Variance Proof for the Filtered Back-Projection

In order to derive the relation between the noise in the image space and the reconstructed noise, we use slightly different notation than we used above for the FBP. Let \( \Delta t, \Delta \theta \) and \( N_\theta \) denote the step size in pixels and angles and the number of angles sampled, respectively. Define the projection as \( m_{ij} = m(t = i\Delta t, \theta = j\Delta \theta) \) such that \( t = x\cos j\Delta \theta + y\sin j\Delta \theta \). Further, let \( \sigma_{max}^2 \geq Var(m(t, \theta)) \) for all \( t \) and \( \theta \). The discrete FBP is then:

\[
I(x, y) = \sum_{ij} m_{ij}g(t - i\Delta t)\Delta t\Delta \theta
\]
Consider then the variance of these reconstructed values and recognizing the filter as a linear operator:

\[ \text{Var}(f(x, y)) = \text{Var} \left( \sum_{i,j} m_{ij} g(t - i\Delta t) \Delta t \Delta \theta \right) = \sum_{i,j} \text{Var}(m_{ij}) g(t - i\Delta t)^2 \Delta t^2 \Delta \theta^2 \]

\[ \leq \sum_{i,j} \sigma_{\text{max}}^2 g(t - i\Delta t)^2 \Delta t^2 \Delta \theta^2 = \sigma_{\text{max}}^2 \Delta t \Delta \theta^2 \sum_{i,j} g(t - i\Delta t)^2 \Delta t \]

Using Parseval’s theorem, applying the Nyquist frequency cutoff for the ramp filter and recognizing that \( \pi \) total degrees are sampled:

\[ \text{Var}(f(x, y)) \leq \frac{\sigma_{\text{max}}^2 \Delta t \Delta \theta^2 N_{\theta}}{12 \Delta t^3} = \frac{\pi^2 \sigma_{\text{max}}^2}{12 N_{\theta} \Delta t^2} \]

This formula provides a reasonable upper bound for the variance in the reconstructed space. Both algorithms performed significantly better than this upper bound of approximately 457 (FBP: 96, EM: 231).

**Sample Size Calculation using Signal to Noise Ratios**

We calculate the relative sample size required to achieve an equivalent effective signal to noise ratio when using an acquisition or processing stream with different statistical power. Let \( \text{SNR}_{\text{EM}}, \text{SNR}_{\text{FBP}}, N_{\text{EM}} \) and \( N_{\text{FBP}} \) be the signal to noise ratio of EM and FBP and the sample size of EM and FBP, respectively. Because standard error is proportional to the square root of sample size, the following equivalence can be assessed:

\[ \text{SNR}_{\text{EM}} \sqrt{N_{\text{EM}}} = \text{SNR}_{\text{FBP}} \sqrt{N_{\text{FBP}}} \]

This equation can trivially be rearranged to show that to achieve the same effective signal to noise ratio, the ratio of the sample sizes must be equal to the square of the inverse of the ratio of the signal to noise ratios. Alternatively, this is equivalent to the inverse of the ratio of the variances. This can be written in functional form as:

\[ \frac{N_{\text{EM}}}{N_{\text{FBP}}} = \left( \frac{\text{SNR}_{\text{FBP}}}{\text{SNR}_{\text{EM}}} \right)^2 = \frac{\text{Var}_{\text{FBP}}}{\text{Var}_{\text{EM}}} \]

Note that these sample size calculations do not incorporate the effect of bias. However, the differences in mean squared error (MSE) parallel these differences in variance.

**Other Ignored Sources of Noise**

In this section, we explain the statistical effect of our simplifying assumptions. The amount of detected photons is, as stated above, Poisson distributed. The intensity of Poisson distributed variables is a radiologic intensity times the length of acquisition times the cross-sectional surface area of the detector array therefore dead time and scan length do not affect our conclusions. Three-dimensional (3D) acquisition increases the cross-sectional surface area of the detector array but does not otherwise have a statistical effect on the Poisson noise. The radiologic intensity decreases over time due to radiological decay. This intensity, however, is approximated to be constant over the scan time, which decreases the contribution of high intensity voxels. The statistical effect of this assumption is not well studied. Similarly, the statistical effect of different reconstruction filters is unclear. Attenuation occurs when dense tissue inside the sample absorbs
photons that pass through the tissue. These absorptions are independent of photon origin; therefore, this uniformly increases the variance of reconstructed intensities. The statistical effect of applying efficient attenuation correction algorithms is unclear. In our simulation, no attenuation occurred; therefore, attenuation correction does not contribute to the results. The amount of random coincidences and scattered photons and the effect of incorrect detector normalization are proportional to the total intensity of the image; therefore, it uniformly increases the variance of reconstructed images. The correction for random coincidences and scatter is improved with 3D images [31,32]. Similarly, interpolation is based upon reconstructed intensities; therefore, it either increases or propagates the effects we describe in our manuscript. Therefore, the ignored factors either uniformly increase the variance of reconstructed intensities or have no effect on our results.