noise. Assuming that

$\rho_{noise(1)}$

is the noise associated density with the first reconstruction, N is the total number of reconstructions and k is the factor by which the volume is increased in each reconstruction by increasing z, then the net noise density of the final averaged reconstruction

$\rho_{net\ noise}$

is given by the following equation:

$$\rho_{net\ noise} = \frac{\rho_{noise(1)}}{N} + \frac{\rho_{noise(1)}}{kN}\left(1 + \frac{1}{2} + \frac{1}{3} + \cdots + \frac{1}{(N-1)}\right)$$

Based on this equation, the first term will decrease because N is in the denominator. The second term has a harmonic series, which is a divergent series, but it also has two terms in the denominator k and N, the product of which will always be larger than the harmonic series, thereby decreasing the overall factor. As such, the overall density of noise will decrease by using EFIRT in 3D reconstructions.

[0031] Figs. 3-7 illustrate an example using EFIRT for 3D reconstructions according to an embodiment of the present invention. In this example, EFIRT is applied to the reconstruction of a protein receptor specimen, the glucocorticoid receptor (GR), from a low-dose Cryo-ET tilt series. Ten reconstructions were performed with the dimensions 250x250x250 to 250x250x700 with z having an incremental increase of 50 grid points. The common region 250x250x250 was cut out from all reconstructions and the average was calculated.

[0032] Fig. 3 shows volume renderings of the initial and final averaged EFIRT reconstructions. As seen in Fig. 3, the 3D reconstruction of this GR sample with EFIRT presents a higher image quality with less noise, as compared to the 3D reconstruction without EFIRT.

[0033] To further visualize the effect of EFIRT, Fig. 4 shows thin slices of both the original and EFIRT averaged reconstructions and the difference between them. Clearly, the EFIRT-applied and averaged reconstruction is less noisy and has an enforced signal with higher SNR, as compared to the original reconstruction ~~401~~. The difference ~~403~~ shows the amount of noise being removed.

[0034] The effect of EFIRT is further illustrated in Fig. 5, which presents the histograms of the original and EFIRT averaged reconstructions and their comparison and difference. As compared to the original histogram, it is clear that the averaged histogram has lower values, thus having a shift towards the left and a higher peak. In the averaged and original histograms, the straight line of values in the beginning is a result of COMET, which converts all negative values to positive. Again, the difference histogram shows the amount of noise being removed.

[0035] In executing the EFIRT procedure for 3D reconstructions, as the value of z increases,

the volume of each successive reconstruction also increases, and the ROI has decreasing information content. As a result, the root mean square (RMS) deviation and mean value of the averaged reconstruction is supposed to be less for each successive reconstruction. This is demonstrated in Fig. 6 showing two graphs: one graph shows the value of the RMS decreasing with respect to the value of z, and the other shows mean value decreasing with respect to the size of z.

[0036] Fig. 7 shows the cumulative density functions (CDF) of the original and the averaged reconstructions. As seen in Fig. 7, the CDF of the averaged reconstruction, i.e., the first curve, goes up faster than the CDF of the original reconstruction, i.e., the second curve. This also shows that the averaged reconstruction has reduced noise.

[0037] Figs. 8-10 illustrate another example using EFIRT for 3D reconstructions according to an embodiment of the present invention. In this example, EFIRT is tested for a non-biological sample, which usually does not experience degradation due to electron exposure during imaging. Eight reconstructions were performed starting with 355x355x255 to 355x355x605 with an increment in z of 50 grid points, and on electron micrographs of SiO_2 nano particles. The common region 355x355x255 was cut out and averaged from all reconstructions.

[0038] Fig. 8 shows the 3D reconstructions of the non-biological sample before and after applying EFIRT. As seen in Fig. 8, the EFIRT-applied reconstruction presents a higher quality than the original reconstruction. The effect of EFIRT is even more obvious in this example because it is not degraded quickly during the TEM imaging, unlike the previous example using a biological sample.

[0039] The effect of EFIRT is further visualized in Fig. 9, where thin slices of the 3D reconstructions of a single SiO_2 nano particle are shown. Compared to the original reconstruction ~~901~~, the EFIRT-applied and averaged reconstruction shows more information and a higher SNR.

Furthermore, Figure 10 shows the histograms of the original reconstruction and the averaged reconstruction and their comparison and difference. As shown in the comparison histogram, it is clear that the averaged histogram has lower values than the original histogram, thus having a shift towards the left and a higher peak. Again, the difference histogram shows the amount of noise being removed.

[0040] Fig. 11 illustrates an algorithm for improved 3D reconstruction images by removing uncorrelated and correlated noises according to an embodiment of the present invention. In brief terms, the algorithm in Fig. 11 comprises two steps: Step 1101, removing shot noise or uncorrelated noise with COMET (constrained maximum relative entropy tomography); and Step 1102, removing correlated noise by applying the EFIRT procedure in 3D reconstructions. In one embodiment, as described above, in Step 1102, the EFIRT is applied by performing a set of reconstructions on an extended

Claims

[Claim 1] A computer implemented method for removing correlated noise by applying Extended Field Iterative Reconstruction Technique (EFIRT) in a three-dimensional (3D) reconstruction, said method comprising:
performing a set of successive reconstructions on an extended field larger than a region of interest (ROI); and
extracting and averaging the ROI from said set of successive reconstructions.

[Claim 2] The computer implemented method according to claim 1, wherein the set of reconstructions is performed by increasing volumes of each successive reconstruction.

[Claim 3] The computer implemented method according to claim 2, wherein the volume of each successive reconstruction is increased by increasing the value of z in the direction of the electron field.

[Claim 4] The computer implemented method according to claim 1, further comprising removing uncorrelated noise in said 3D reconstruction with COMET (constrained maximum relative entropy tomography).

[Claim 5] The computer implemented method according to claim 1, wherein the 3D reconstruction is implemented via a Cryo-Electron Tomography (Cryo-ET) application.

[Claim 6] The computer implemented method according to claim 1, wherein the 3D reconstruction is applied to a biological sample or a non-biological sample.

[Claim 7] A system for removing correlated noise in a three-dimensional (3D) reconstruction by applying Extended Field Iterative Reconstruction Technique (EFIRT), said system comprising:
a processor; and
a memory accessible to said processor, wherein said processor is programmed to execute executable instructions stored in said memory, said executable instructions, while executed, causing said processor to:
perform a set of successive reconstructions on an extended field larger than a region of interest (ROI); and
extract and average the ROI from said set of successive reconstructions.

[Claim 8] The system according to claim 7~~1~~, wherein said executable instructions, while executed, further causing said processor to perform the set of reconstructions by increasing volumes of each successive reconstruction.

[Claim 9] The system according to claim 8, wherein the volume of each