doi:10.1017/S143192761700469X
Microsc. Microanal. 23 (Suppl 1), 2017

Cryo-STEM Tomography with Inpainting

Andrew Stevens[1,2] and Nigel D. Browning[1,3]

[1.] Duke University, Dept. of Electrical and Computer Engineering, Durham, NC, USA
[2.] Pacific Northwest National Laboratory, Richland, WA, USA
[3.] University of Washington, Dept. of Materials Science and Engineering, Seattle, Washington, USA

Traditionally, microscopists have worked with the Nyquist-Shannon theory of sampling, which states that to be able to reconstruct the image fully it needs to be sampled at a rate of at least twice the highest spatial frequency in the image. This sampling rate assumes that the image is sampled at regular intervals and that every pixel contains information that is crucial for the image (it even assumes that noise is important). Images in general, and especially low dose S/TEM images, contain significantly less information than can be encoded by a grid of pixels (which is why image compression works). Mathematically speaking, the image data has a low dimensional or sparse representation. Through the application of compressive sensing methods [1,2,3] this representation can be found using pre-designed measurements that are usually random for implementation simplicity. These measurements and the compressive sensing reconstruction algorithms have the added benefit of reducing noise.

This reconstruction approach can be extended into higher dimensions, whereby the random sampling in each 2-D image can be extended into: a sequence of tomographic projections (i.e. tilt images); a sequence of video frames (i.e. incorporating temporal resolution and dynamics); spectral resolution (i.e. energy filtering an image to see the distribution of elements); and ptychography (i.e. sampling a full diffraction image at each location in a 2-D grid across the sample). This approach has been employed experimentally for materials science samples requiring low-dose imaging [2], and can be readily applied to biological samples.

Figure 1 shows the resolution possible in a complex biological system, mouse pancreatic islet beta cells [4], when tomogram slices are reconstructed using subsampling. Reducing the number of pixels (1/6 pix and 1/3*1/3) shows minimal degradation compared to the reconstructions using all pixels (all data and 1/3 tilt). Although subsampling 1/6 of the tilts (1/6 of overall dose) degrades the reconstruction to the point that the cellular structures cannot be identified. Using 1/3 of both the pixels and the tilts provides a high quality image at 1/9 the overall dose even for this most basic and rapid demonstration of the CS methods. Figure 2 demonstrates the theoretical tomogram reconstruction quality (vertical axis) as undersampling (horizontal axis) is increased; we examined subsampling pixels and tilt-angles individually and a combined approach in which both pixels and tilts are sub-sampled. Note that subsampling pixels maintains high quality reconstructions (solid lines).

Using the inpainting algorithm to obtain tomograms can automatically reduce the dose applied to the system by an order of magnitude. Perhaps the best way to understand the impact is to consider that by using inpainting (and with minimal hardware changes), a sample that can normally withstand a dose of ~10 e/Å^2 can potentially be imaged with an "equivalent quality" to a dose level of 10^3 e/Å^2. To put this in perspective, this is approaching the dose level used for the most advanced images, in terms of spatial resolution, for inorganic systems. While there are issues for biological specimens beyond dose (structural complexity being the most important one), this sampling approach allows the methods that are traditionally used for materials science to be applied to biological systems [5].

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[5] Supported by the Chemical Imaging, Signature Discovery, and Analytics in Motion Initiatives at PNNL. PNNL is operated by Battelle Memorial Inst. for the US DOE; contract DE-AC05-76RL01830.

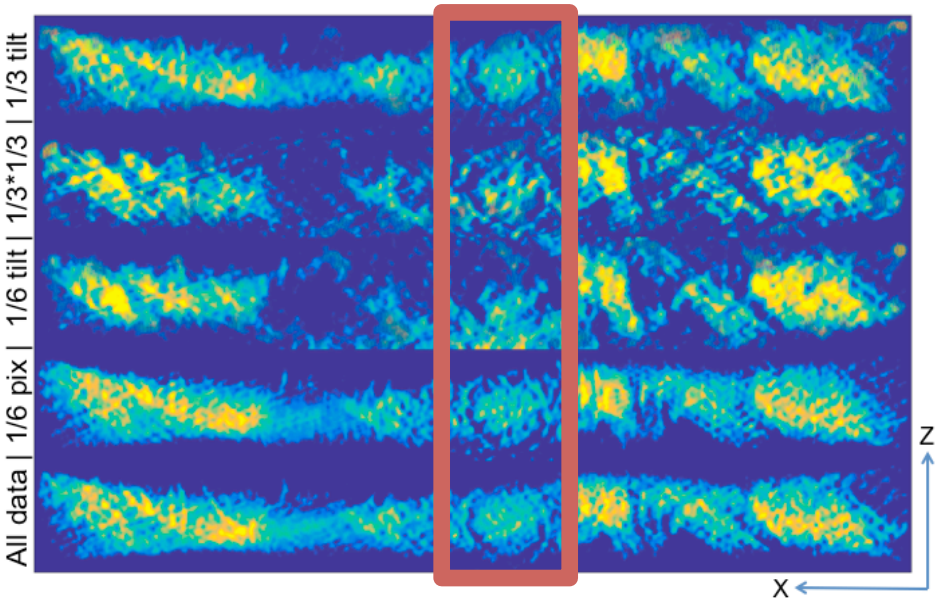

Figure 1. Visual comparison of mouse beta cell tomogram slice reconstructions. Reducing the number of pixels (1/6 pix and 1/3*1/3) shows minimal degradation compared to full pixel reconstructions (all data and 1/3 tilt). Subsampling 1/6 of the tilts degrades the reconstruction so that the cellular structures cannot be identified, whereas equivalent pixel subsampling is comparable to using all of the data.

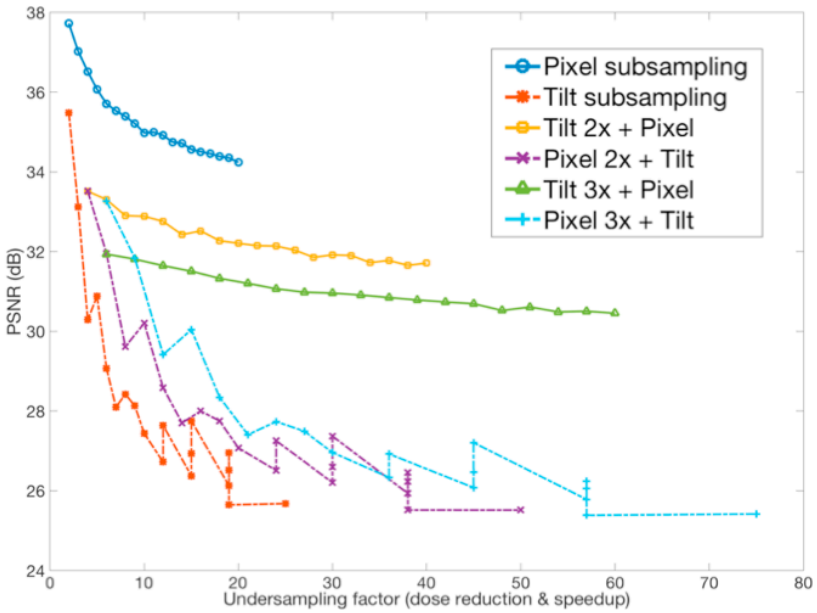

Figure 2. Quantitative results showing that dose can be reduced without sacrificing image quality.

https://doi.org/10.1017/S143192761700469X Published online by Cambridge University Press