Matthew Applegate
Department of Electrical Engineering
Northeastern University
360 Huntington Street
Boston, MA 02115

October 25, 2022

Subject: Submission of manuscript entitled, **"Self-supervised denoising of Nyquist sampled volumes via deep learning"**

To the Editor:

Please find attached a copy of our manuscript "Self-supervised denoising of Nyquist sampled volumes via deep learning" to be considered for publication in the *Journal of Biomedical Optics*.

In recent years deep learning has demonstrated enhanced performance over traditional methods in many areas of research, including medical imaging. Many deep learning algorithms for image processing are supervised, meaning they need examples of the completed task to learn from. For image denoising, this requires paired images, one clean, and one noisy, for training. Collecting pairs of images in this manner requires careful co-registration and time-consuming imaging protocols that are impractical for the vast majority of medical imaging modalities for reasons of cost, patient comfort, and safety. There is a substantial need for effective denoising algorithms that are self-supervised, meaning they do not require access to clean versions of the image to be denoised.

In this work we present a new self-supervised denoising algorithm that can effectively remove noise from a variety of common medical imaging modalities without the need for a co-registered clean versions of the training set, or any special data collection protocols. This algorithm, which we call "noise2Nyquist," takes advantage of correlation between adjacent frames in a volumetric image stack to remove noise. We use a simulated noise-free example to show that errors that arise from using adjacent images depend on the sampling rate and are relatively small, so long as the volume is sampled at, or above, the Nyquist frequency.

We go on to demonstrate the effectiveness of noise2Nyquist on confocal microscopy images of cell nuclei collected with low laser power, simulated low-dose CT images of liver metastases, and noisy OCT images of human skin collected *in vivo*. We find that the performance of noise2Nyquist is competitive with supervised methods without the need for clean versions of the images. Noise2Nyquist outperforms "noise2void," a popular self-supervised denoising algorithm; "neighbor2neighbor," a newer self-supervised algorithm; as well as many conventional filters. Overall, noise2Nyquist provides excellent denoising performance on volumetric data sampled at the Nyquist rate or higher, and can be trained on any existing dataset without the need for special instrumentation or data collection protocols. This work significantly increases the utility of machine learning methods by relaxing the stringent requirements associated with supervised machine learning techniques. We believe this manuscript will be of interest to readers of *IEEE Transactions of Medical Imaging*.

This work has not been copyrighted, published, submitted, or accepted for publication elsewhere.

Thank you for your consideration, please do not hesitate to contact us if you require further information.

Sincerely,

Matthew Applegate, on behalf of the
authors