Deep learning enables long-term gentle super resolution imaging

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Abstract

Long term imaging of dynamic subcellular phenomena in living cells is limited by phototoxicity and photobleaching. This problem is exacerbated in microscopes with higher spatiotemporal resolution, particularly super-resolution imaging. The machine learning approach presented here aims to drastically reduce the amount of light required to image intracellular protein dynamics with structured illumination microscopy (SIM). As we show, for selected protein distributions, our approach allows acquisition of over 10,000 images (600 imaging volumes) without significant photobleaching, without appreciably compromising signal-to-noise ratio (SNR) or spatial resolution, and without making any modification to the underlying microscope hardware.

Training image pairs using Deep Residual Channel Attention Networks (RCAN)

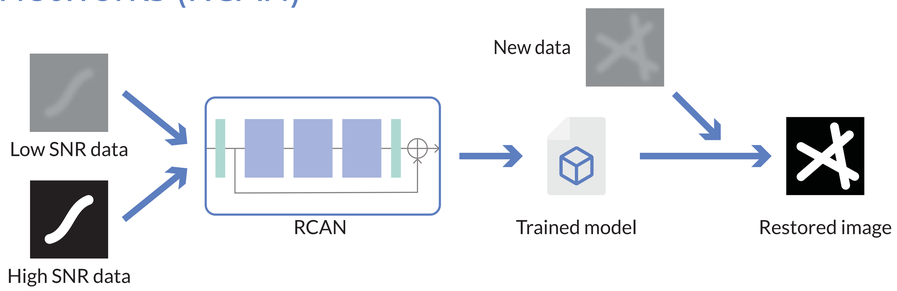

Figure 1. 36 image pairs of low- and high-quality images of fluorescently-labeled actin were used to train the model. The DL model is based on the RCAN architecture [1] which learns to statistically relate intrinsic features between the image pairs. The model can be applied to new data similar to the input images.

RCAN enhances and restores images captured with low laser power

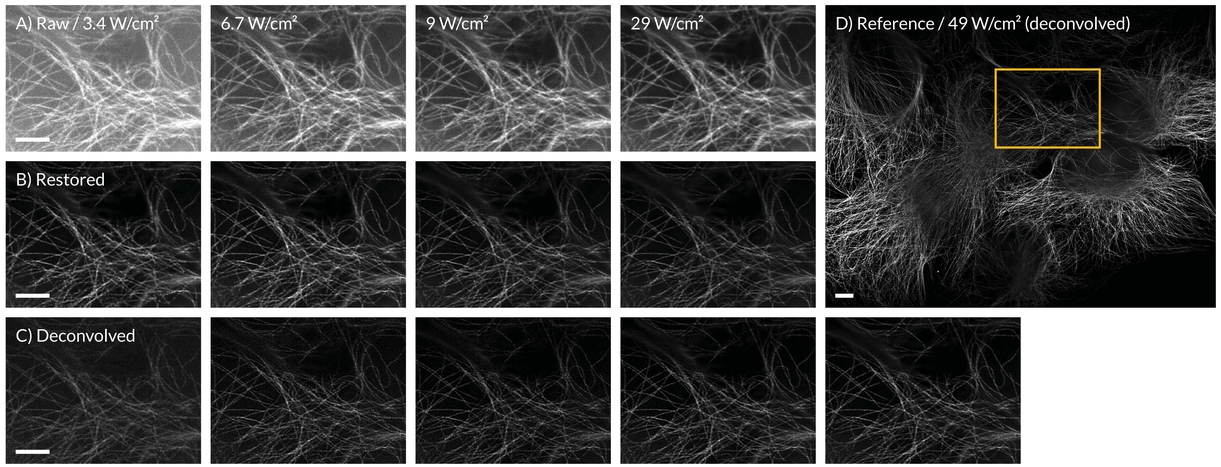

Figure 2. Training images (not shown) were acquired on an instant structured illumination microscope (iSIM) [2] with image dimension of 1,920 x 1,550 x 14 voxels. The training images were captured at excitation power levels of 3.4, 6.7, 9, 13, 29, 49 W/cm² and the ground truth image at 370 W/cm² followed by deconvolution. The trained model was applied to raw 3D images above (A) that had been acquired on the iSIM with a range of low excitation power conditions. The restored images (B) compare favorably in image quality and resolution to the deconvolved images (C), and are comparable to the reference image (D), which was acquired at 49 mW/cm² with deconvolution applied, even at the lowest power settings. Visual qualification of the results validates the trained model for improving image quality and resolution. Scale bar = 5 µm

RCAN enables gentle, long-term imaging of mitochondria by iSIM

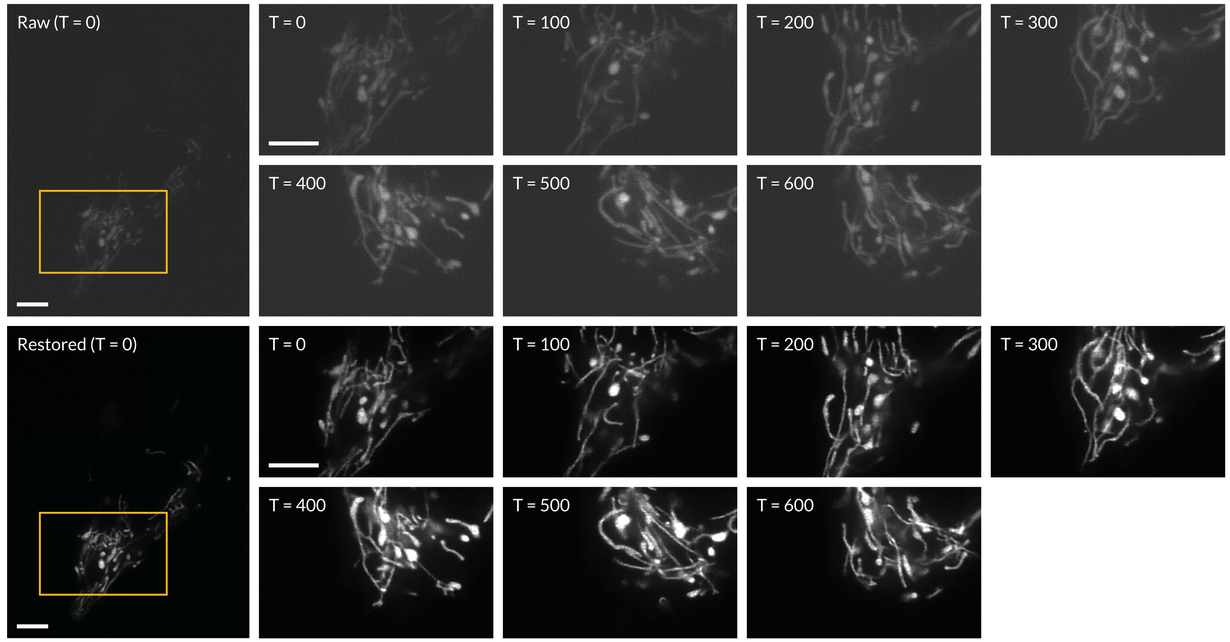

Figure 3. Long-term imaging of cells with labeled mitochondria consisting 600 volumetric time points was acquired on an iSIM system at low excitation power (20 W/cm²) to dramatically limit phototoxicity and photobleaching of the sample. The RCAN model trained using only fluorescent-labled actin was applied to restore the whole raw image sequence. The restored sequence showed significant improvement to the signal-to-noise ratio (SNR) and resolution of the raw image. Moreover, as no mitochondria data was used to train the model, the restored image sequence validates the general applicability of the presented model for restoring images that were acquired with low excitation power. While routine live cell iSIM imaging is done at ~100 W/cm² of excitation power which limits the recording length, the proposed approach enables acquisition at reduced power for extended term imaging without compromising image quality. Scale bar = 5 µm

Summary and acknowledgement

The present deep learning-enabled approach provides microscopists with a new solution for the problem of phototoxicity and photobleaching. We have demonstrated that:

- The model can restore images acquired at relatively low excitation power to resolution similar to the ground truth
- The model can be applied to long (600 volumetric time points) live cell recordings using reduced excitation power
- The model has general applicability for improving SNR and image resolution for fluorecently-labeled actin or mitochondria, using only actin-labeled cells as training data

While the input images were unusable for quantitative or qualitative analysis, the DL-restored images are of similar quality to the ground truth such that further image analysis could be possible. The presented approach enables imaging and quantitative analysis of long-term live cell recordings. The research is funded in part by U.S. National Institute of Neurological Disorders and Stroke Grant #5R44NS097094-03.

References

1. Y Zhang, et al. (2018) Image super-resolution using very deep residual channel attention networks. arXiv preprint, arXiv:1807.02758.
2. AG York, et al. (2013) Instant super-resolution imaging in live cells and embryos via analog image processing. Nat Methods 10, 1122-1126.