Deep Learning Based Super-Resolution

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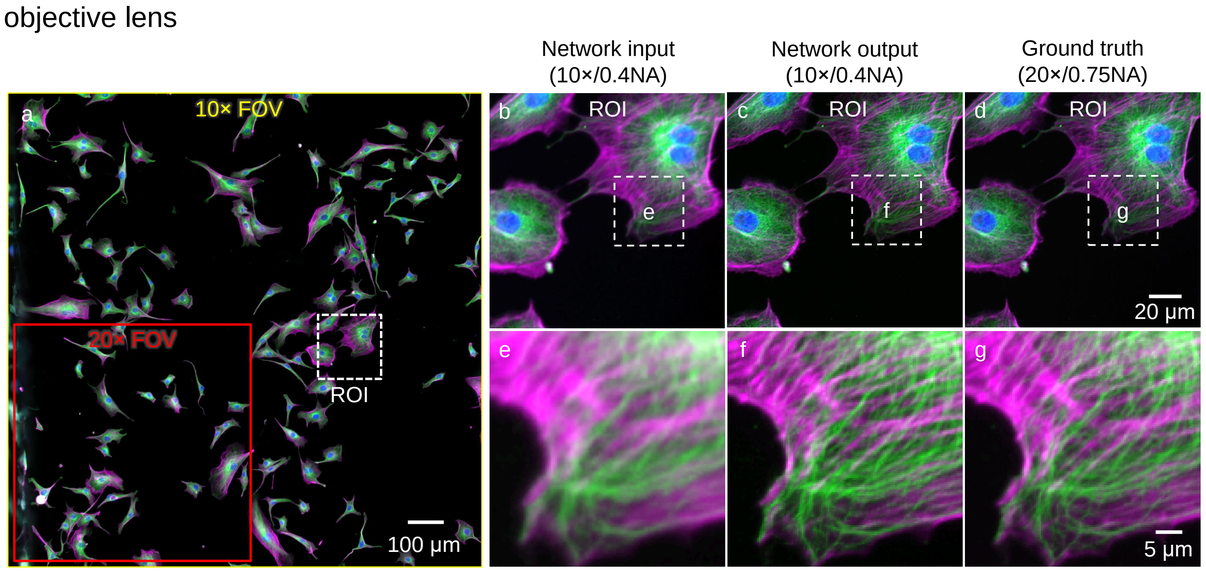
Introduction

We present a deep learning-enabled cross-modality image transformation framework that super-resolves a single input image acquired by a diffraction-limited microscope to match the resolution of an image acquired using a super-resolution microscope [1]. Our framework is based on a conditional generative adversarial network (GAN), and is purely data-driven, i.e. the deep neural network model is trained with pre-registered low- and high-resolution images pairs, without any prior knowledge of the image formation model or a point-spread-function (PSF). The pre-trained network model infers high-resolution images in a non-iterative way without any parameter search. We demonstrated our framework's super-resolution imaging capabilities using various microscopy modalities. This deep learning-enabled approach has the potential to democratize access to various high-resolution imaging modalities that are normally restricted to well-resourced labs.

Super-resolved images of bovine pulmonary artery endothelial cells

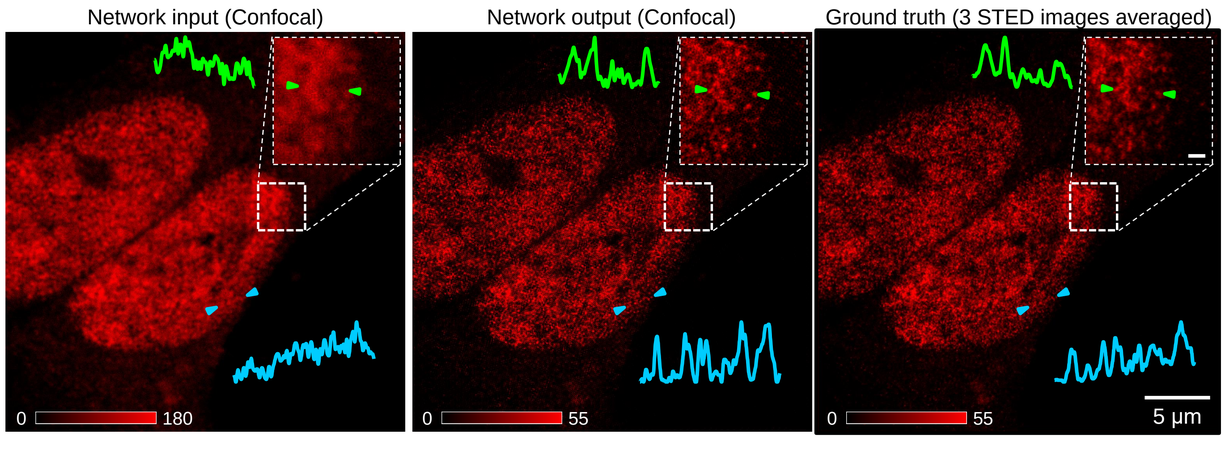
First, for wide-field microscopy, images that were captured with a 10x/0.4NA objective lens were super-resolved to match the resolution of the images captured with a 20x/0.75NA objective lens



The figure above shows the resolution enhancement of BPAEC intracellular structures by applying a pretrained deep neural network to each color channel of the input images. (a) Network input image from 10×/0.4NA objective lens. A small ROI is zoomed-in and shown in (b) network input, (c) network output, and (d) ground truth (20×/0.75NA). (e-g) Further zoom-in on a cell's F-actin and microtubules corresponding to each image in (b-d).

Cross-modality image transformation from confocal to STED

We then demonstrated confocal to Stimulated Emission Depletion (STED) microscopy cross-modality transformation, where the confocal images of 20 nm fluorescent particles and Histone3 distributions with HeLa cell nuclei were super-resolved to match the resolution of the images captured with a STED microscope.

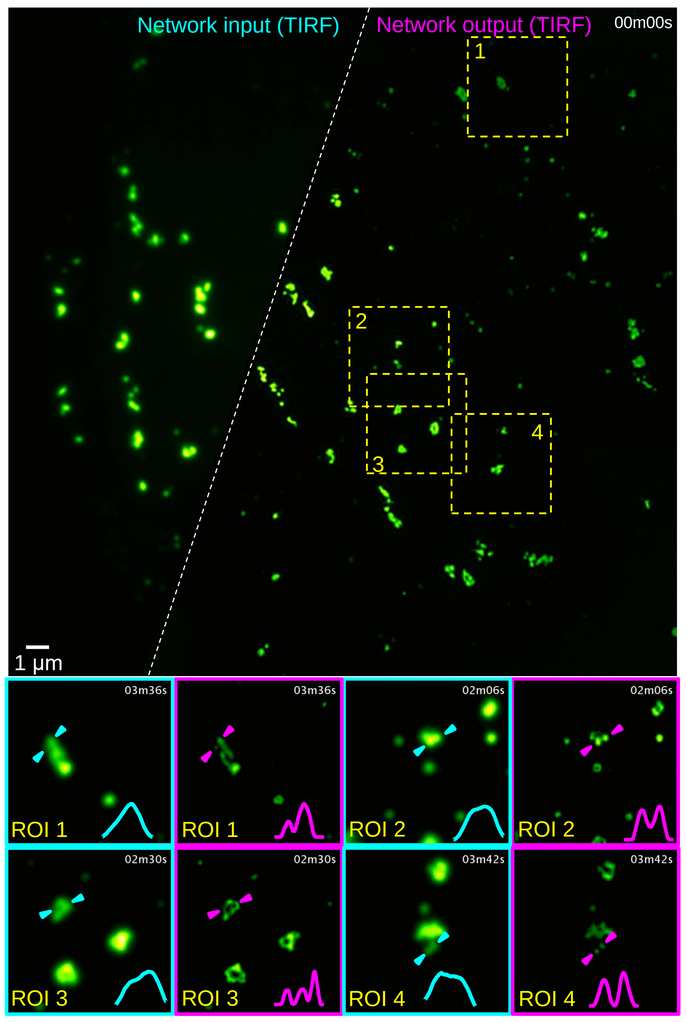


The figure above shows deep-learning enabled cross-modality image transformation from confocal to STED. A diffraction-limited confocal microscope image of Histone 3 distributions within HeLa cell nuclei is used as input to the neural network to blindly yield the network output image, which is comparable to a STED image of the same FOV. Three individual STED scans of the same FOV, averaged to create the right panel. Scale bar in the inset in the right panel is 500 nm and applies to all insets. Arrows in each image refer to the line of the shown cross-section.

Cross-modality image transformation from TIRF to TIRF-SIM

Finally, we applied our framework to Total Internal Reflection Fluorescence (TIRF) based imaging of eGFP expressed by gene edited SUM159 cells to reveal endocytic clathrin-coated structures, matching the image resolution obtained with a TIRF-based Structured Illumination Microscope (i.e., TIRF-SIM). [2]

In these experiments, the sample was exposed to nine different structured illumination patterns following a reconstruction method used in SIM. The right image shows the deep-learning enabled cross-modality image transformation from TIRF to TIRF-SIM. On the top is a TIRF image of a gene-edited SUM159 cell expressing AP2-eGFP. The network model super-resolves the diffraction-limited TIRF image and matches TIRF-SIM reconstruction results.

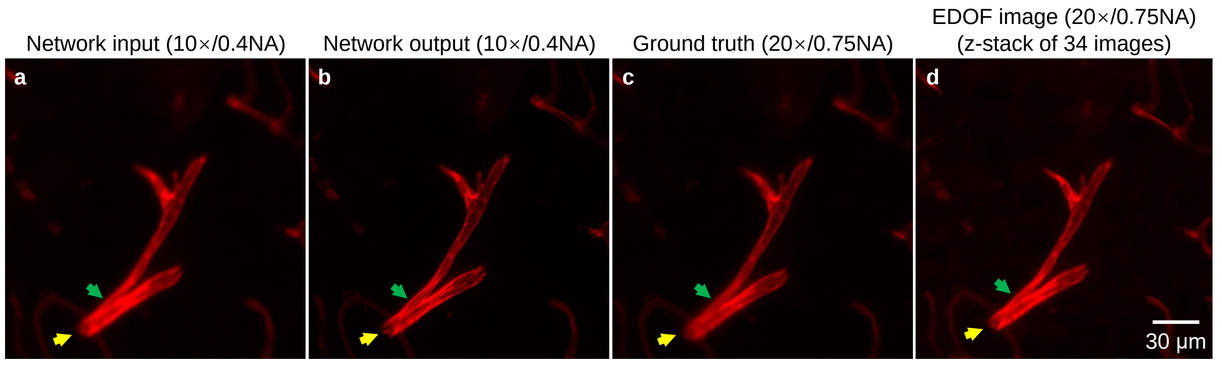


Zoomed-in regions of at the labeled ROIs and time points are enlarged below. The generalizability of the inference of this network was demonstrated on a new type of sample (amnioserosa tissues of a Drosophila embryo) that it has never seen before. Scale bar in the lower-right inset image represents 500 nm.

To highlight some examples, the neural network was able to detect the dissociation of clathrin-coated pits from larger clathrin patches as shown in inset figure, as well as the development of curvature-bearing clathrin cages. These results demonstrate that our network model can super-resolve individual clathrin-coated structures within cultured cells and tissues of a developing metazoan embryo.

Model generalization and extended depth-of-focus

The images that were inferred using the deep neural network also demonstrate a larger depth-of-field and a better signal-to-noise-ratio, compared to the ground truth images. Further quantitative analysis (e.g., spatial frequency response, artifact analysis, PSF analysis, and differential image analysis [1]) confirmed the frequency extrapolation properties of our network to achieve super-resolution across different modalities.



The output image from a single input image is demonstrated and compared to extended-DOF image. This experiment was only performed once, as this is a unique 3D sample that better reveals the extended-DOF feature of our network.

References

[1]. Wang, H. *et al.* Deep learning enables cross-modality super-resolution in fluorescence microscopy. *Nature Methods* **16**, 103 (2019).

[2]. Li, D. et al. Extended-resolution structured illumination imaging of endocytic and cytoskeletal dynamics. *Science* **349**, aab3500 (2015).

Acknowledgements

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