High-fidelity fluorescence image restoration using deep unsupervised learning

Xinyang Li,[1,2] Zhifeng Zhao,[1] Guoxun Zhang,[1] Hui Qiao,[1] Haoqian Wang,[2] and Qinghai Dai[1]
[1]*Department of Automation, Tsinghua University, Beijing 100084, China*
[2]*Tsinghua Shenzhen International Graduate School, Tsinghua University, Shenzhen, 518055, China*
Correspondences: daiqh@tsinghua.edu.cn;

Abstract: Current deep learning methods for fluorescence image restoration necessitate numerous well-aligned image pairs for training. We develop an unsupervised learning framework for high-fidelity fluorescence image restoration without the laborious work of image annotation and registration.

1. Introduction

Deep neural networks (DNNs) [1] have shown its powerful capabilities in optical microscopy and play an important role in promoting biological research [2]. One of the most common applications of deep learning in fluorescence microscopy is image restoration, i.e., reconstructing high-quality images from degraded images. Mathematically, this image-to-image transformation task can be modeled as nonlinear pixel-wise regression that maps a pixel intensity in the source image to another reasonable pixel value in the target image with reference of neighborhood information [3]. Many network architectures have been demonstrated to be versatile for image-to-image transformation [4-6]. However, these DNNs are based on supervised learning and vast amounts of images and corresponding annotations are needed to be collected. The success of these networks usually needs time-consuming data acquisition and laborious annotations and registrations [7].

Recently, the invention of cycle-consistent generative adversarial networks (CycleGAN) [8] makes unsupervised training of convolutional neural networks (CNNs) possible. But the applications of CycleGAN are confined to simple classification tasks like segmentation [9] because complex regression would confuse the network and mislead it to converge to biased mappings.

To advance the feasibility of this unsupervised learning framework in optical microscopy, here, we introduce content-preserving cycle-consistent generative adversarial network (c^{2}GAN) for unsupervised fluorescence image restoration. We demonstrate its competitive performance in several image restoration tasks by comparison with the ground truth, as well as the results of conventional CNN trained with paired training data.

2. Methods and results

CycleGAN is an emerging deep learning framework based on unsupervised learning, which simultaneously trains a pair of reciprocal generative adversarial networks (GANs). After proper training, one image in the source domain could be mapped back after the sequential processing of the twin GANs (as shown in Fig. 1(a)). However, some

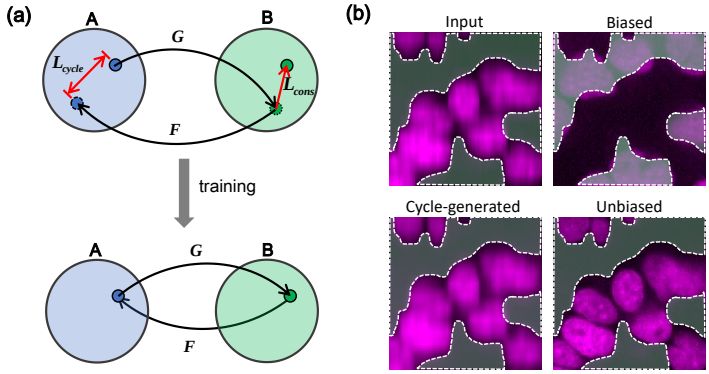

Fig. 1. Schematic of c^{2}GAN. (a) *A* and *B* represent the source domain and the target domain, respectively. A forward GAN (*G*) and a backward GAN (*F*) are simultaneously trained to establish a pair of reciprocal mappings. The cycle-consistency loss (L_{cycle}) and structural loss (L_{cons}) are enforced to guarantee cycle consistency and high fidelity, respectively. (b) The GANs are likely to converge to biased mappings without the structural loss.

biased mappings could be learned because the original objective function is not tight enough (as shown in Fig. 1(b)). To shrink the solution space to a tighter range and exclude unwanted solutions, we impose an additional structural constraint term to confine the location of the object in the output image. This reinforced objection function can guarantee fast and stable convergence and accurate mappings in most conditions.

We test the performance of c^{2}GAN on a typical denoising task that maps low-SNR (signal to noise ratio) images of Planaria, a kind of light-sensitive worm commonly used in the research of cell regeneration, to high-SNR images to avoid phototoxicity caused by high excitation dose. The training data is based on the released data of Weigert *et al* [5] and the images are processed to ensure that there are no aligned images in the two domains. The test results are shown in Fig. 2(a) that the output image of c^{2}GAN is quite similar to the corresponding ground truth. We also compare the performance of c^{2}GAN with that of conventional supervised CNN [5]. The high-SNR images are better restored by c^{2}GAN because no saturation occurs. For better visualization, we plot the intensity distribution histograms of the images as shown in Fig. 2(b). It is clear that the intensity distribution is well preserved and no pixel saturation and distribution deformation occur, which demonstrates c^{2}GAN's capability of high-fidelity fluorescence image restoration. This method can be extended to other applications that can be modeled as pixel-wise regression. Our framework opens up new possibilities for the use of deep unsupervised learning in the field of optical microscopy.

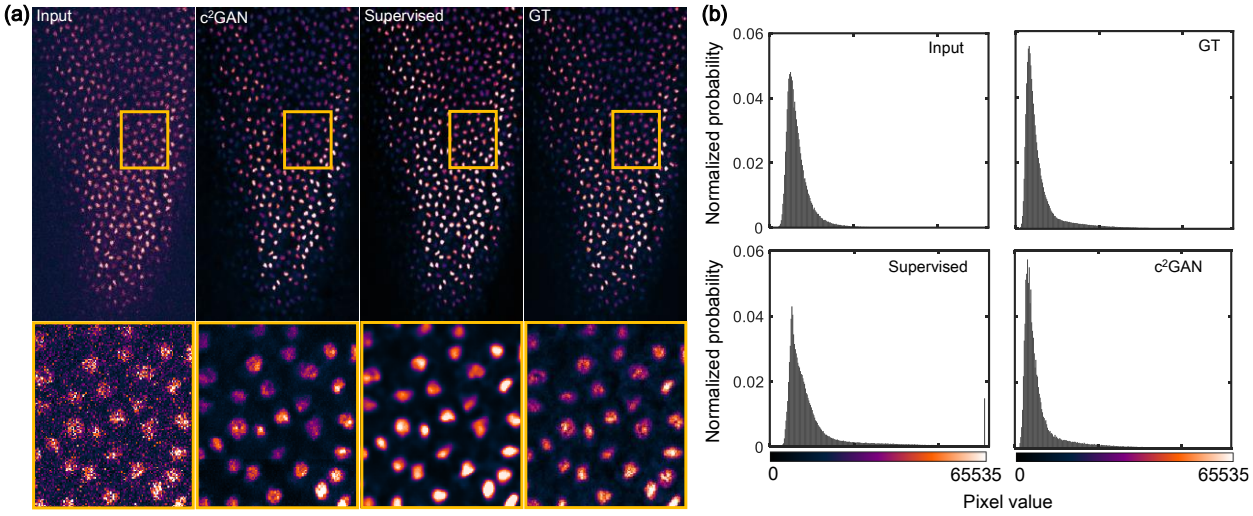

Fig. 2. High-fidelity fluorescence image restoration with c^{2}GAN. (a) The input and the output of c^{2}GAN, as well as the results of the supervised CNN and corresponding ground truth. (b) Statistical histograms of images in (a). The distribution of c^{2}GAN's results is in high consistency with the ground truth while the image fidelity of supervised CNN is degraded to some extent. In the output of conventional supervised CNN, a certain percentage of pixels are saturated (pixel value=65535).

3. References

[1] Y. LeCun, Y. Bengio, and G. Hinton, "Deep learning," Nature **521**, 436-444 (2015).
[2] E. Moen, D. Bannon, T. Kudo, W. Graf, M. Covert, and D. Van Valen, "Deep learning for cellular image analysis," Nat Methods (2019).
[3] H. Zhao, O. Gallo, I. Frosio, and J. Kautz, "Loss Functions for Image Restoration With Neural Networks," Ieee Trans Comput Im **3**, 47-57 (2017).
[4] T. Falk, D. Mai, R. Bensch, O. Cicek, A. Abdulkadir, Y. Marrakchi, A. Bohm, J. Deubner, Z. Jackel, K. Seiwald, A. Dovzhenko, O. Tietz, C. Dal Bosco, S. Walsh, D. Saltukoglu, T. L. Tay, M. Prinz, K. Palme, M. Simons, I. Diester, T. Brox, and O. Ronneberger, "U-Net: deep learning for cell counting, detection, and morphometry," Nat Methods **16**, 67-70 (2019).
[5] M. Weigert, U. Schmidt, T. Boothe, A. Muller, A. Dibrov, A. Jain, B. Wilhelm, D. Schmidt, C. Broaddus, S. Culley, M. Rocha-Martins, F. Segovia-Miranda, C. Norden, R. Henriques, M. Zerial, M. Solimena, J. Rink, P. Tomancak, L. Royer, F. Jug, and E. W. Myers, "Content-aware image restoration: pushing the limits of fluorescence microscopy," Nat Methods **15**, 1090-1097 (2018).
[6] H. D. Wang, Y. Rivenson, Y. Y. Jin, Z. S. Wei, R. Gao, H. Gunaydin, L. A. Bentolila, C. Kural, and A. Ozcan, "Deep learning enables cross-modality super-resolution in fluorescence microscopy," Nature Methods **16**, 103-+ (2019).
[7] C. Belthangady and L. A. Royer, "Applications, promises, and pitfalls of deep learning for fluorescence image reconstruction," Nat Methods (2019).
[8] Zhu, J.-Y., Park, T., Isola, P. & Efros, A. A. Unpaired image-to-image translation using cycle-consistent adversarial networks. In *Proc. IEEE International Conference on Computer Vision* 2223–2232 (IEEE, 2017).
[9] S. J. Ihle, A. M. Reichmuth, S. Girardin, H. Han, F. Stauffer, A. Bonnin, M. Stampanoni, K. Pattisapu, J. Vörös, and C. Forró, "Unsupervised data to content transformation with histogram-matching cycle-consistent generative adversarial networks," Nature Machine Intelligence **1**, 461-470 (2019).