Advancing a Computational Miniature Mesoscope

Fluorescence microscopy is essential for studying biological structures and dynamics. Existing systems, however, suffer from a trade-off between field of view (FOV), resolution and system complexity, and cannot fulfill the emerging need for miniaturized platforms providing micron-scale resolution across centimeter-scale FOVs.

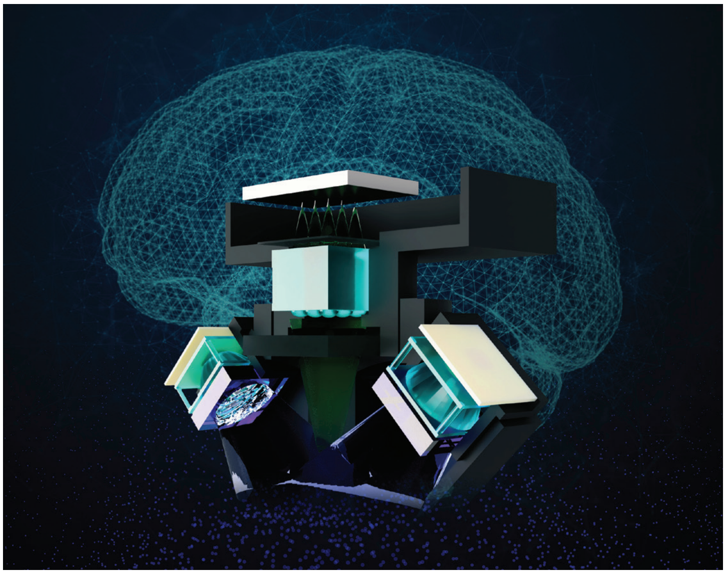
To overcome this challenge, two years ago, we developed a computational miniature mesoscope (CM^2) that exploits a computational imaging strategy to enable single-shot, 3D high-resolution imaging across a wide FOV in a miniaturized platform.[1] In work published this year, we further advanced CM^2 technology by integrating novel miniature optics and deep learning.[2]

The CM^2 achieves its single-shot 3D imaging capability via a microlens array (MLA). To achieve high image contrast, in version two of the system, we designed a hybrid emission filter to suppress undesired spectral leakage. In addition, we designed and 3D-printed a miniature freeform LED collimator, which is compact and lightweight, to provide greater than 80% excitation efficiency. Built around a back-side-illuminated CMOS sensor, CM^2 version two achieved a fivefold improvement in image contrast over the version-one system, and captures high-SNR measurements in various experimental conditions.

Our deep-learning model, CM^{2}Net, achieved high-quality 3D recovery across a wide FOV with high 3D resolution and fast reconstruction speed. CM^{2}Net is designed based on the multi-view geometry of the CM^2. The model solves the single-shot 3D reconstruction problem using three functional modules. The “view demixing” module de-multiplexes the 3×3 views from the MLA. The “view-synthesis” and “light-field refocusing enhancement” modules jointly perform high-resolution 3D reconstruction. In addition, to incorporate 3D linear-shift variant (3D-LSV) information into CM^{2}Net, we developed a low-rank 3D-LSV model to efficiently generate realistic CM^2 measurements, which are used to train the CM^{2}Net.

We showed that CM^{2}Net, trained using 3D-LSV simulator, generalized well to experiments and was robust to variations in the emitter’s local contrast and SNR. CM^{2}Net enhanced the axial resolution to around 25 μm—eight times better than the model-based reconstruction. The 3D reconstructions were validated against tabletop widefield measurements. In addition, CM^{2}Net reduced the reconstruction time to less than 4 s for a volume spanning a 7-mm FOV and a 0.8-mm depth, showing a speed roughly 1,400 times faster and a memory cost around 19 times less than the model-based algorithm.

Overall, our contribution is a novel deep-learning-augmented computational miniaturized microscope that achieves single-shot, high-resolution (roughly 6 μm lateral and 25 μm axial resolution) 3D fluorescence imaging across a mesoscale FOV. We expect that this simple, low-cost miniature system—built using off-the-shelf and 3D-printed components—will be useful in a wide range of large-scale 3D fluorescence-imaging and neural-recording applications. OPN



Artist’s interpretation of an updated version of the CM^2 computational miniature mesoscope, which integrates new miniature optics and deep learning.

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REFERENCES

1. Y. Xue et al. Sci. Adv. **6**, eabb7508 (2020).
2. Y. Xue et al. Optica **9**, 1009 (2022).