

## **Single Molecule Localization by Interferometric & Cryogenic Imaging**

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Remarkable progress in Single molecule localization microscopy (SMLM) has been made in the past decade. Here I would like to present interferometric and cryogenic imaging which exhibit excellent localization precision performances compared to conventional SMLMs. We introduced interferometric SMLMs named ROSE and ROSE-Z. A fluorescence molecule is located by the intensities of multiple excitation patterns of an interference fringe, providing improvement in the localization precision compared to the conventional centroid fitting method at the same photon budget. We demonstrate this technique by resolving a nanostructure down to 5 nm. We also built an ultra-stable super-resolution cryo-FM that exhibits excellent thermal and mechanically stability. We have demonstrated the super-resolution imaging capability of this system. The results suggest that our system is particularly suitable for SMLM and cryogenic super-resolution correlative light and electron microscopy. Based on the cryo-fluorescence imaging technique we developed, we build a cryogenic correlated light, ion and electron microscopy (cryo-CLIEEM) that is capable of preparing cryo-lamellae under the guidance of three-dimensional confocal imaging. Moreover, we demonstrate a workflow to preselect and preserve nanoscale target regions inside the finished cryo-lamellae. By successfully preparing cryo-lamellae that contain a single centriole or contact sites between subcellular organelles, we show that this approach is generally applicable, and shall help in innovating more applications of cryo-ET.

### References:

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