Three dimensional nanoscopy of whole cells and tissues with *in situ* point spread function retrieval

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Single molecule localization microscopy, as a typical type of super resolution microscopy, has overcome the diffraction limit and provided unprecedented opportunities for biologists to observe organelle structures, interactions, and protein functions at the nanoscale level. However, imaging whole cells and tissues is still challenging since the inhomogeneous refractive indices inside the specimen distort the fluorescent signal emitted by single-molecule probes, and therefore, rapidly deteriorate the resolution with the increasing depth. Here we propose a method that enables the construction of an *in situ* 3D response of single emitters directly from single molecule blinking datasets and therefore allows for pin-pointing their locations with Cramér-Rao lower bound achieving precision and uncompromised fidelity. This method is demonstrated across a range of cellular and tissue architectures from mitochondrial networks and nuclear pores in mammalian cells, to amyloid β plaques and dendrites in brain tissues, and elastic fibers in developing cartilage of mice. This advancement expands the applicability of single molecule localization microscopy from selected cellular targets near coverslips to intra- and extra-cellular targets deep inside tissues.