Super-Resolution Microscopy across Arbitrary Scales

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Microscopy has facilitated the discovery of many biological insights by optically magnifying images of small structures in fixed cells and tissues. Much effort has been invested, accordingly, in the design and implementation of lenses of increasing refracting power and quality. We here report that physical magnification of the specimen itself is possible.

Polymerizing electrolyte monomers directly within a sample into an electrically charged polymer network, followed by dialysis in pure water, results in expansion of the polymer network into extended conformations, and thus specimen expansion. By covalently anchoring specific molecules within the specimen to this polymer network and proteolytically digesting endogenous biological structure, we found that samples could be expanded isotropically ~4.5-fold in linear dimension.

We discovered that this isotropic expansion applies to nanoscale structures, and thus this method, which we call expansion microscopy (ExM), can effectively separate molecules located within a diffraction limited volume, to distances great enough to be resolved with conventional microscopes. Thus, this process can be used to perform scalable super-resolution microscopy with diffraction limited microscopes.

ExM represents a new modality of magnification, and enables scalable, multi-color super-resolution imaging of fixed cells and tissues. Unlike many other super-resolution methods, ordinary dyes can be imaged, enabling multicolor imaging with conventional dyes. Since the expansion is isotropic in all directions, our resolution improvement applies to axial as well as lateral directions. Since the expanded sample is mostly water, it is transparent. We demonstrate ExM in both cultured cells and intact brain tissue, performing three-color super-resolution imaging of ~10^7 μm^3 of the mouse hippocampus with a conventional confocal microscope, achieving ~70 nm lateral resolution.