

**Metallo-Supramolecular Branched Polymer Protects Particles from Air-water Interface in
Single-Particle Cryo-Electron Microscopy**

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Recent technological breakthroughs in single-particle cryo-electron microscopy (cryo-EM) enabled rapid atomic structure determination of biological macromolecules. A major bottleneck in the current single particle cryo-EM pipeline is the preparation of good quality frozen cryo-EM grids, which is mostly a trial-and-error process. Among many issues, preferred particle orientation and sample damage by air-water interface (AWI) are common practical problems. Here we reported a method of applying metallo-supramolecular branched polymer (MSBP) in the cryo-sample preparation for high-resolution single-particle cryo-EM. Our data shows that MSBP keeps a majority of particles away from air-water interface and mitigates preferred orientation as verified by the analyses of apoferritin, hemagglutinin (HA) trimer and various sample proteins. The use of MSBP is a simple method to improve particle distribution for high-resolution structure determination in single-particle cryo-EM.