

Building Laboratory-on-Tip for Imaging Biological Samples with Atom Probe Tomography

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Knowledge acquired by various high-resolution imaging techniques, such as electron microscopy (EM) and confocal imaging, has been crucial for the fundamental understanding of cell biology as well as engineering of novel biomaterials. Based on a very different principle, field ion microscopy (FIM) developed in 1960 once promised a new route to explore the chemical compositions of biomolecules [1]. Further incorporation of the position sensitive detector allows atom probe tomography (APT) to reconstruct the 3D evaporated volume at near atomic resolution. Application has been extended to cellular samples including mammalian and bacterial cells [2-3]. Compared to routine APT studies on metallic samples, imaging biological samples with APT requires two well planned stages:

- *Biological sample preparation.* Considering the high content of water, protocols are routinely required ranging from plunge freezing which helps maintaining the near-native state, to disruptive resin embedding. Chemical fixation may also be needed due to biosafety requirements, which has been known to alter the chemical structure of the samples. An appropriate balance between equipment/skill availability and the expected details of chemical information needs to be determined prior to studying biological samples with APT.

- *APT sample preparation and transfer.* The broader application of APT to biology, however, is largely limited by this challenge. One requirement for APT experiments is that the radius of the final tip needs to be less than 75 nm. We have been developing novel approaches including: (1) optimizing physical vapor deposition (PVD) for conductive coating of insulated and low conductivity APT samples [4]; (2) engineering 2D material (graphene) to “encapsulate” the biological samples followed by APT imaging [5], and (3) nanofabrication approaches to manipulate the APT samples towards high-throughput analysis and correlative imaging with cryo-EM. All these achievements lay a foundation for building a “laboratory-on-tip” to enable APT imaging of subcellular targets as well as environmentally-sensitive materials [6].

References:

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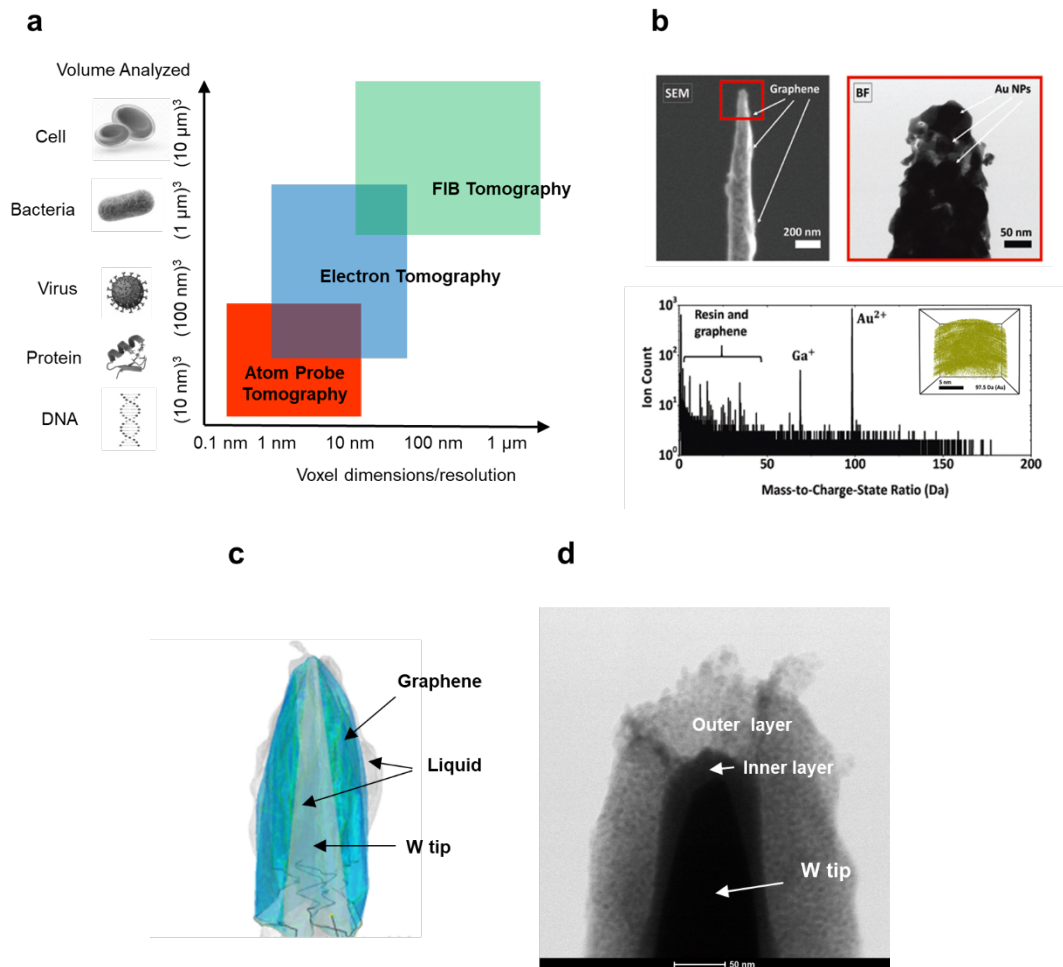


Figure 1. (a) An overview of 3D tomography methods for biological samples by resolution and volume analyzed. (b) EM images and APT reconstruction of resin-embedded Au nanoparticle enhanced with graphene encapsulation [5]. (c) Computer simulation result showing the dynamic process of encapsulating liquid with single layer graphene, and (d) TEM image of a liquid APT sample structured with multiple layers of graphene.