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Structural Biology in the Liquid State: Shedding Light on Protein Dynamics

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Liquid phase electron microscopy LP EM offers remarkable capabilities with regards to imaging time resolved structures in their native liquid media by removing the artefacts caused by traditional drying or cryogenic treatments. One of the most exciting applications of LP EM is the investigation of cell molecular machinery structures such as proteins. The liquid nature of the sample offers novel opportunities such as accessing previously inaccessible protein states or the possibility of 3D structure reconstruction by applying tomographic methods. Image reconstruction in liquid-state poses several challenges, and most importantly, it undermines the single-particle analysis assumption stating that the three-dimensional objects captured by the detector are identical over time. Indeed, the free movement of soft objects in LP EM grants the opportunity of screening the protein structural landscape during the imaging process. Such feature provides a unique selling point of the technique for structural biology investigations.

We propose the combination of all-atom simulations with LP EM to complement protein structural studies with dynamic investigations. We employed LP EM to image proteins in solution exploiting their natural rotation with the aim of accessing the particle structural landscape. Tomographic techniques were employed for reconstructing protein architecture in 3D. The use of LTEM for the investigation of proteins is not limited to 3D reconstruction and structural analysis. We have also employed LP EM to investigate Amyloid-β (Aβ) aggregation. Aβ is a small, disordered protein. Aβ accumulates into stages of microscopic amyloid oligomers, fibres and plaques that are found in brains affected by Alzheimer's disease (AD). The details of the aggregation pathway remain elusive, with much of current knowledge arising from computational simulations. Preliminary investigations on Aβ aggregation, via LP EM will be presented. This work, although still in early stages, promises to provide relevant and novel biological information on Aβ aggregation pathways.