

4D transmission electron microscopy: imaging soft materials and biologicals in liquid phase

Giuseppe Battaglia

Department of Chemistry, Institute of Structural and Molecular Biology, Institute for the Physics of Living Systems, and EPSRC/JEOL Centre for Liquid Phase Electron Microscopy, University College London, London, UK.

Institute for Bioengineering of Catalonia (IBEC), The Barcelona Institute for Science and Technology (BIST), Barcelona, Spain.

Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain

Water is a critical component for both function and structure of soft matter and it is what bestows the adjective soft. Imaging samples in liquid state is thus paramount to gathering structural and dynamical information of any soft materials. Herein we propose the use of liquid phase electron microscopy to expand ultrastructural analysis into dynamical investigations. We imaged several soft materials including vesicles, micelles, gels as well as several proteins in liquid phase using transmission electron microscopy and demonstrate that the inherent Brownian motion associated with the liquid state can be exploited to gather three-dimensional information of the materials in their natural state. We call such an approach Brownian tomography (BT). We combine BT with single particle analysis (Brownian particle analysis BPA) to image protein structures with a spatial resolution close that achievable using cryogenic TEM. We show that BPA allows sub-nanometre resolution of soft materials and enables to gather information on conformational changes, hydration dynamics, and the effect of thermal fluctuations.

Relevant references:

G. Marchello, C. De Pace, A. Duro-Castano, G. Battaglia, and L. Ruiz-Perez End-to-end image analysis pipeline for liquid-phase electron microscopy *Journal of Microscopy*, Vol. 279, Issue 3 2020, pp. 242–248
G. Marchello, C. De Pace, N. Wilkinson, L. Ruiz-Perez, G. Battaglia *arXiv* preprint arXiv:1907.03348