Molecular dynamics simulation of the Brownian motion of biomolecules in liquid phase electron microscopy

Mr Xiaopeng Wu[1], Dr Peng Wang[1]
[1]Department of Physics, University of Warwick, Coventry, United Kingdom

Background incl. aims
Liquid phase electron microscopy (LP-EM) revolutionizes our ability to observe dynamic processes within liquids at nanoscale resolution. It allows for the direct observation of biological, chemical and physical phenomena in their native liquid environments which was not possible with conventional or cryogenic electron microscopy (Cryo-EM). While previous successes of the technique have predominantly been demonstrated with rigid materials such as gold nanoparticles [1], it is anticipated that the application of the technique on soft materials such as biological macromolecules may yield novel insights into the functioning mechanisms from the observed dynamics [2].

In this work, we aim to investigates the behaviour of biomolecular samples in a liquid environment and consider the effect of the Brownian motion.

Methods
We employed molecular dynamics simulations to study the behaviour of the biomolecules in liquid at the nanosecond scale. The structure of the horse liver alcohol dehydrogenase (ADH) enzyme was used for this study [3], as shown in figure (a). We simulated multiple trajectories of the ADH enzyme using the OpenMM library [4], and the ff14SB force field along with the TIP3P water model was used for all simulations [5].

Results
As expected, the diffusivity of the protein is found to be increasing with temperature from the simulations. The protein exhibits significant deviations due to Brownian motion, which can be characterised by a random walk model, in figure (b), we have shown a snippet of the trajectory of the centre of mass of the ADH at 300 K to confirm that the global motion of the protein is indeed random. When the thermal energy of the water molecules is low but still above the freezing point, the diffusive motion of the protein tends to favour the direction with the smallest solvent accessible surface area, this was due to the irregular shape of the ADH protein. Upon further increase of temperature to 300 K, this anisotropy diminishes, as the protein diffuses more isotopically potentially due to more frequent interactions between the solvent and itself.

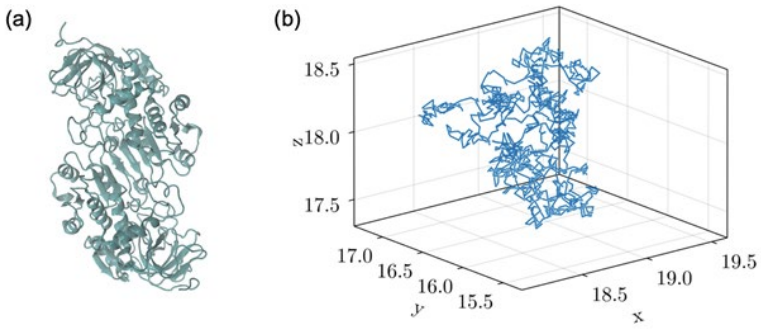
The protein exhibits thermal vibrations across all temperatures, which collectively influence the overall deviation of its structure. These vibrations

are temperature-dependent and exhibit a relatively stable magnitude throughout the period of observation. Additionally, higher temperatures can induce further localised deviations within the protein structure, particularly in regions with higher flexibility, such as the sequence termini, where deviations can be notably pronounced compared to the rest of the protein.

Conclusion

Overall, this study enhances our understanding of the effect of Brownian motion inherent to biomolecules in liquid and may inform the development of more effective experimental designs for LP-EM. Future studies could extend this analysis to samples of different configurations, as well as longer simulation times for more robust estimations over larger timescales. The authors would like to acknowledge funding from the BBSRC International Institutional Partnership Fund.

Graphic:



Keywords:

Liquid-phase, electron microscopy, molecular dynamics

Reference:

[1] Wu, H., Friedrich, H., Patterson, J. P., Sommerdijk, N. A. J. M. & Jonge, N. de. Liquid-Phase Electron Microscopy for Soft Matter Science and Biology. Advanced Materials 32, 2001582– 2001583 (2020)
[2] Zheng, H., Claridge, S. A., Minor, A. M., Alivisatos, A. P. & Dahmen, U. Nanocrystal Diffusion in a Liquid Thin Film Observed by in Situ Transmission Electron Microscopy. Nano Lett. 9, 2460–2465 (2009)
[3] Herzik, M. A., Wu, M. & Lander, G. C. High-resolution structure determination of sub-100 kDa complexes using conventional cryo-EM. Nat Commun 10, 1032–1033 (2019)
[4] Eastman, P. et al. OpenMM 7: Rapid development of high performance algorithms for molecular dynamics. PLOS Computational Biology 13, e1005659 (2017)
[5] Maier, J. A. et al. ff14SB: Improving the Accuracy of Protein Side Chain and Backbone Parameters from ff99SB. J. Chem. Theory Comput. 11, 3696–3713 (2015)