

**Fast Viral Dynamics Revealed by Microsecond Time-Resolved Cryo-EM**S. V. Barrass<sup>1,2</sup>, O. F. Harder<sup>1</sup>, M. Drabbels<sup>1</sup>, U. J. Lorenz<sup>1\*</sup><sup>1</sup>Ecole Polytechnique Fédérale de Lausanne (EPFL), Laboratory of Molecular Nanodynamics; CH-1015 Lausanne, Switzerland, <sup>2</sup>Sarah.Barrass@epfl.ch

Observing proteins as they perform their tasks has largely remained elusive, which has left our understanding of protein function fundamentally incomplete. To enable such observations, we have recently proposed a novel technique that improves the time resolution of cryo-electron microscopy (cryo EM) to microseconds [1-5]. We demonstrate for the first time that microsecond time-resolved cryo-EM enables observations of fast protein dynamics [6]. We use our approach to elucidate the capsid mechanics of cowpea chlorotic mottle virus (CCMV), whose large-amplitude motions play a crucial role in the viral life cycle [6]. We observe that a pH jump causes the extended configuration of the capsid to contract on the microsecond timescale. While this is a concerted process, the motions of the capsid proteins involve different timescales, leading to a curved reaction path.

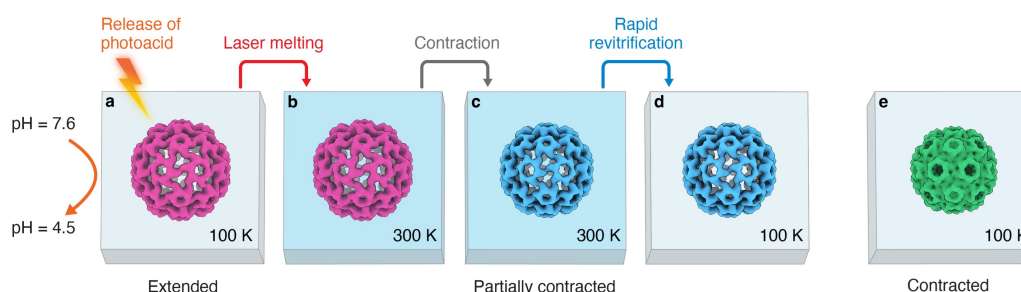


Fig. 1. Microsecond time-resolved cryo-EM of the CCMV contraction — experimental concept.

- [1] J. M. Voss, O. F. Harder, P. K. Olshin, M. Drabbels, U. J. Lorenz, *Struct. Dyn.*, **2021**, 8, 054302  
[2] J. M. Voss, O. F. Harder, P. K. Olshin, M. Drabbels, U. J. Lorenz, *Chem. Phys. Lett.*, **2021**, 778, 138812  
[3] O. F. Harder, J. M. Voss, P. K. Olshin, M. Drabbels, U. J. Lorenz, *Acta Crystallogr. Sect D. Struct. Biol.*, **2022**, 78, 883-889  
[4] G. Bongiovanni, O. F. Harder, M. Drabbels, U. J. Lorenz, *Front. Mol. Biosci.*, **2022**, 9, 1044509  
[5] G. Bongiovanni, O. F. Harder, J. M. Voss, M. Drabbels, U. J. Lorenz, *Acta Crystallogr. Sect D. Struct. Biol.*, **2023**, 79, 473-478  
[6] Oliver F. Harder, Sarah V. Barrass, Marcel Drabbels, Ulrich J. Lorenz, *bioRxiv*, **2023**, 19.536710