LS-O5: Nguyen Thi Hong Ha

Email: tnguyen31@hawk.iit.edu

Symmetry-Breaking Mechanisms of the SARS-CoV-2 Main Protease

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Hong Ha Nguyen, James Tufts, David D. L. Minh*

**Department of Chemistry, Illinois Institute of Technology, Chicago, IL 60616, USA*

The coronavirus 3C-like main protease (MPro) – an essential target of COVID-19 drugs – has approximately half of the activity and an asymmetric dimer structure at certain pH, suggesting that only one catalytic site is active at a time. However, the mechanism that leads to this asymmetry is unknown. Prior to the COVID-19 pandemic, previous modeling studies that investigated the asymmetry of MPro were only about 148 ns long. In the last few years, several groups have produced much longer simulations of MPro and released them to the public for detailed analysis. Here, we analyze a 100-microsecond simulation produced by D.E. Shaw Research (DESRES) and a series of trajectories with an aggregate time of 2.9-millisecond produced by Folding@Home to investigate the mechanism by which asymmetry emerges. The D.E. Shaw simulation reveals a domino chain initiated by breaking the salt-bridge Arg4*-Glu290 that propagates to alternate conformations of the catalytic sites. Markov state model analysis of the Folding@Home simulations reveals that transitions between active and inactive conformations in two subunits are reversible and that one subunit is preferentially in an active conformation.