The Conformational Space of the SARS-Cov-2 Main Protease Active Site Loops Is Determined by Ligand Binding and Interprotomer Allostery

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We characterize two SARS-CoV-2 main protease (M^{pro}) active site loops using all-atom molecular dynamics simulations on a microsecond timescale. Dimensionality reduction and clustering are used to identify open and closed ensembles in both the upper and lower loops, as well as an additional intermediate ensemble in the lower loop. Closed and intermediate ensembles stabilize the positions of the catalytic Cys-His dyad and bring an Asp in position to mediate charge from a proton transfer during catalysis. Simulating a protease-substrate mimetic complex increases the frequency of closed and intermediate states and reveals that a substrate binding to one protomer of the homodimer causes its apo partner to more closely resemble the bound ensemble. We use dynamic network analysis to reveal the optimal allosteric path between active sites, which travels through a pathway bridged by the N-terminus. This study offers insight into relationships between the disordered loops and substrate binding in the M^{pro}.