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Atomistic Simulations of the pH Induced Functional Rearrangement of Influenza Hemagglutinin XINGCHENG LIN, Rice Univ, JEFFREY NOEL, Max Delbruck Center for Molecular Medicine, QINGHUA WANG, JIANPENG MA, Baylor Colledge of Medicine, JOSE ONUCHIC, Rice Univ — Influenza hemagglutinin (HA), a surface glycoprotein responsible for the entry and replication of flu viruses in their host cells, functions by starting a dramatic conformational rearrangement, which leads to a fusion of the viral and endosomal membranes. It has been claimed that a loop-to-coiled-coil transition of the B-loop domain of HA drives the HA-induced membrane fusion. On the lack of dynamical details, however, the microscopic picture for this proposed "spring-loaded" movement is missing. To elaborate on the transition of the B-loop, we performed a set of unbiased all-atom molecular dynamics simulations of the full B-loop structure with the CHARMM36 force field. The complete free-energy profile constructed from our simulations reveals a slow transition rate for the B-loop that is incompatible with a downhill process. Additionally, our simulations indicate two potential sources of kinetic traps in the structural switch of the B-loop: Desolvation barriers and non-native secondary structure formation. The slow timescale of the B-loop transition also confirms our previous discovery from simulations using a coarse-grained structure-based model, which identified two competitive pathways both with a slow B-loop transition for HA to guide the membrane fusion.

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