Supporting information for:

Energetics of Flap Opening in HIV-1 Protease: String Method Calculations

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Correlation between ligand unbinding and elbow engagement

By observing normal movements during ligand unbinding, the correlation between ligand movement out of the pocket and elbow engagement is apparent. Fig. S1 shows the evolution of two independent TAMD simulations and the correlation between ligand unbinding and elbow engagment. In Fig. S1A, the elbows quickly engaging which allows the ligand to exit the pocket within several ns. Within 10 ns, the ligand has fully exited the pocket and the elbows relax to their natural *apo* state. In Fig. S1B, the elbows do not immediately engage and the ligand remains trapped in the binding pocket for over 10 ns. Once the elbows engage, the ligand quickly exits the pocket and the elbows disengage to their natural state. Through these representative time traces, the necessity of elbow engagement and

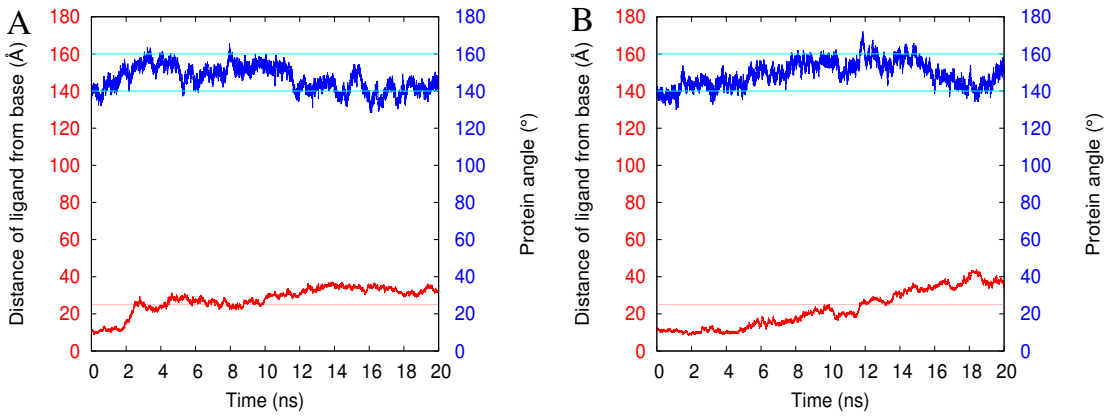

Figure S1: Ligand movement out of the binding pocket (red) and quaternary angle (blue) observed over 20 ns WT-TAMD$_{\text{holo}}$ simulations. The quaternary angle is shown in blue with the relaxed *apo* (open) ($\approx 160°$) and fully closed ($\approx 140°$) states shown in cyan. The distance from the center of the ligand to the protein base is shown in red with the approximate distance to fully exit the pocket ($\approx 25\mathring{A}$) shown in pink.

F99Y mutation alters protein movement during TAMD

Protein movements and interactions during ligand unbinding is altered through a F99Y mutation. Fig. S2A shows the state of the quarternary angle throughout the ligand unbinding event. The protein does not visit the engaged elbow state during the ligand unbinding event in contrast to WT

PR. In Fig. S2B, the distance of the flaps from the base is shown for the same F99Y-TAMD$_{\mathrm{holo}}$ simulation as a function of time. The flaps form the fully open state early in the simulation as the ligand exits the pocket but around 8 ns, the flaps reestablish interactions to form into the slightly open state. This reformation of the slightly open state was not seen in any instances during WT-TAMD simulations.

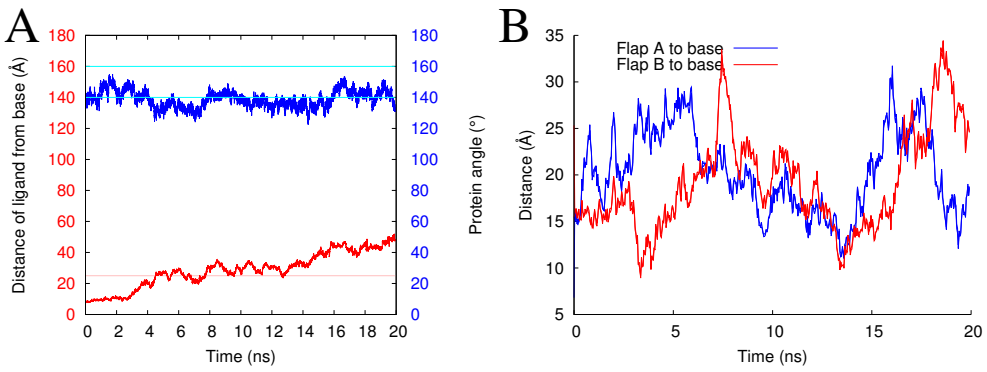

Figure S2: Effect of F99Y mutation on natural movements of PR. A: Time trace of the distance of the ligand from the base of the protein (red) and quaternary angle (blue). B: Distance of flaps from base of protein over time.