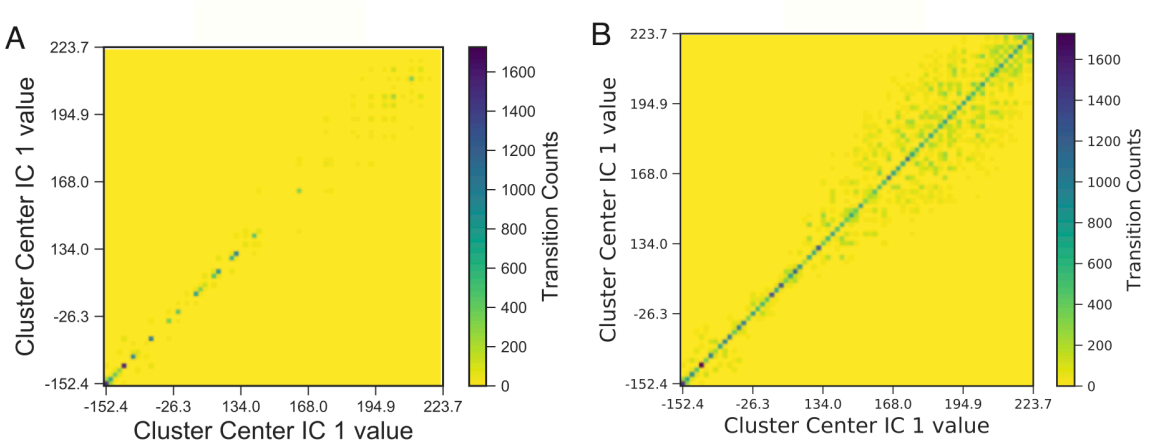


**Figure S1. Improvement in Transitions-based Sampling from Adaptive Sampling. Related to STAR Methods.**

MSM transitions counts matrix ordered by the cluster tIC1 value. A) Matrix based upon only the Anton trajectories. B) Matrix using all data that went into final MSM.

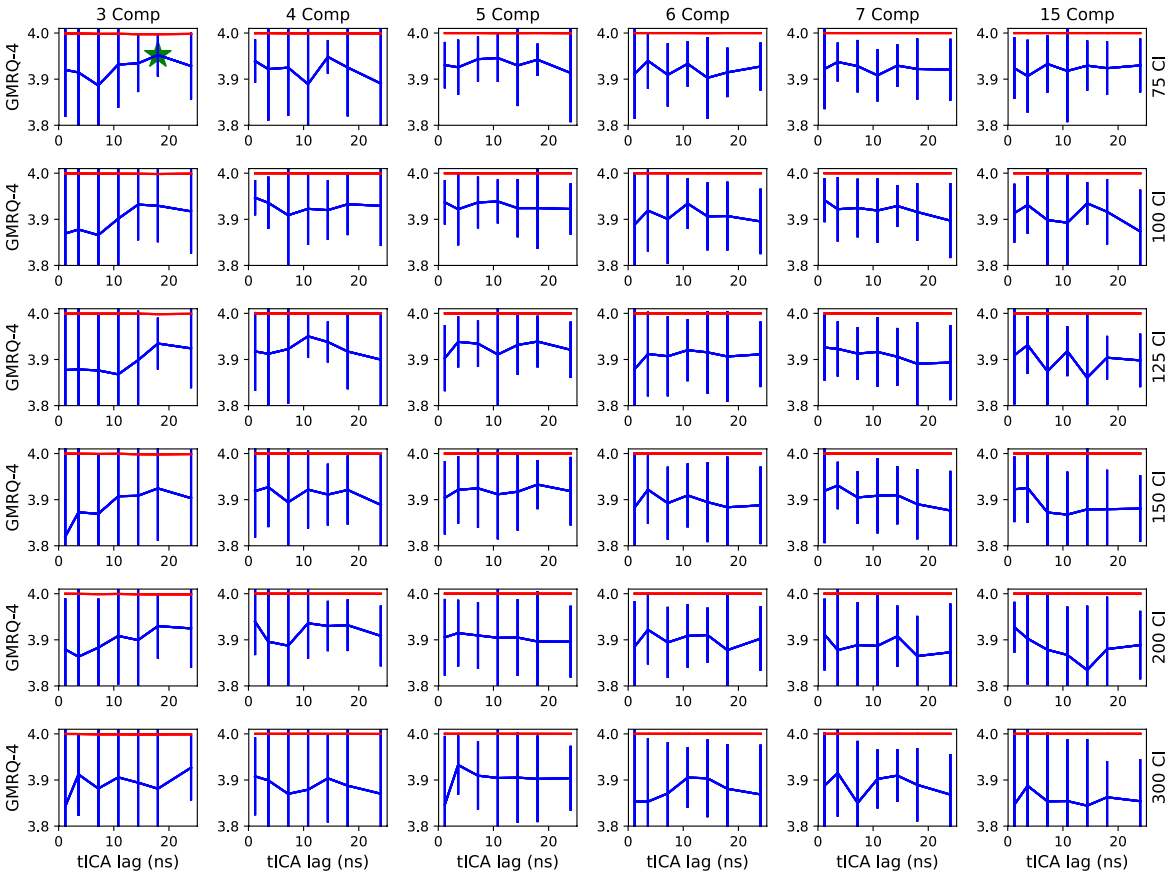


**Figure S2. GMRQ Analysis for MSM Parameter Selection. Related to Figure 4.** GMRQ score for training set (red) and validation set (blue) for different tica lag times, number of tica components, and number of clusters.

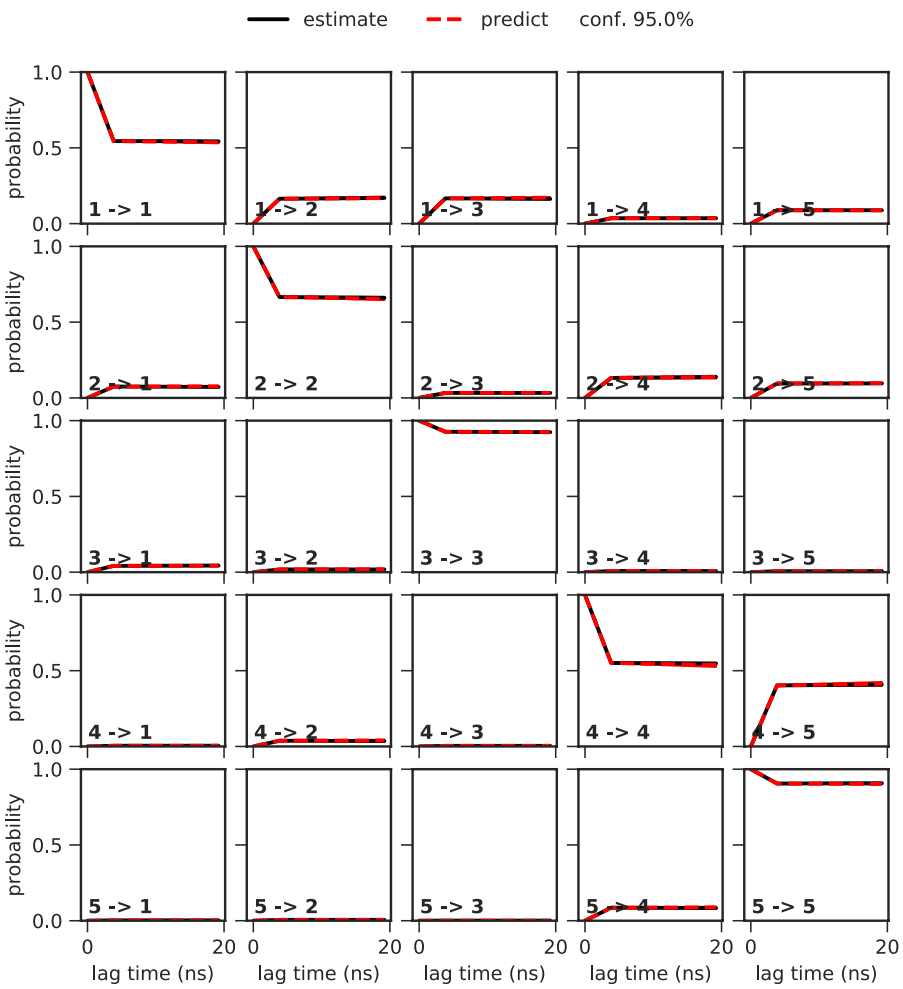


**Figure S3. Chapman-Kolmogorov Test on Macrostate Transitions Probabilities. Related to Figure 4.**

Chapman–Kolmogorov test, showing the transition probabilities between the 5 macrostates for predictions made by propagating the original model (red dashed) and estimation made by a new transition matrix made at lag times kτ (black).

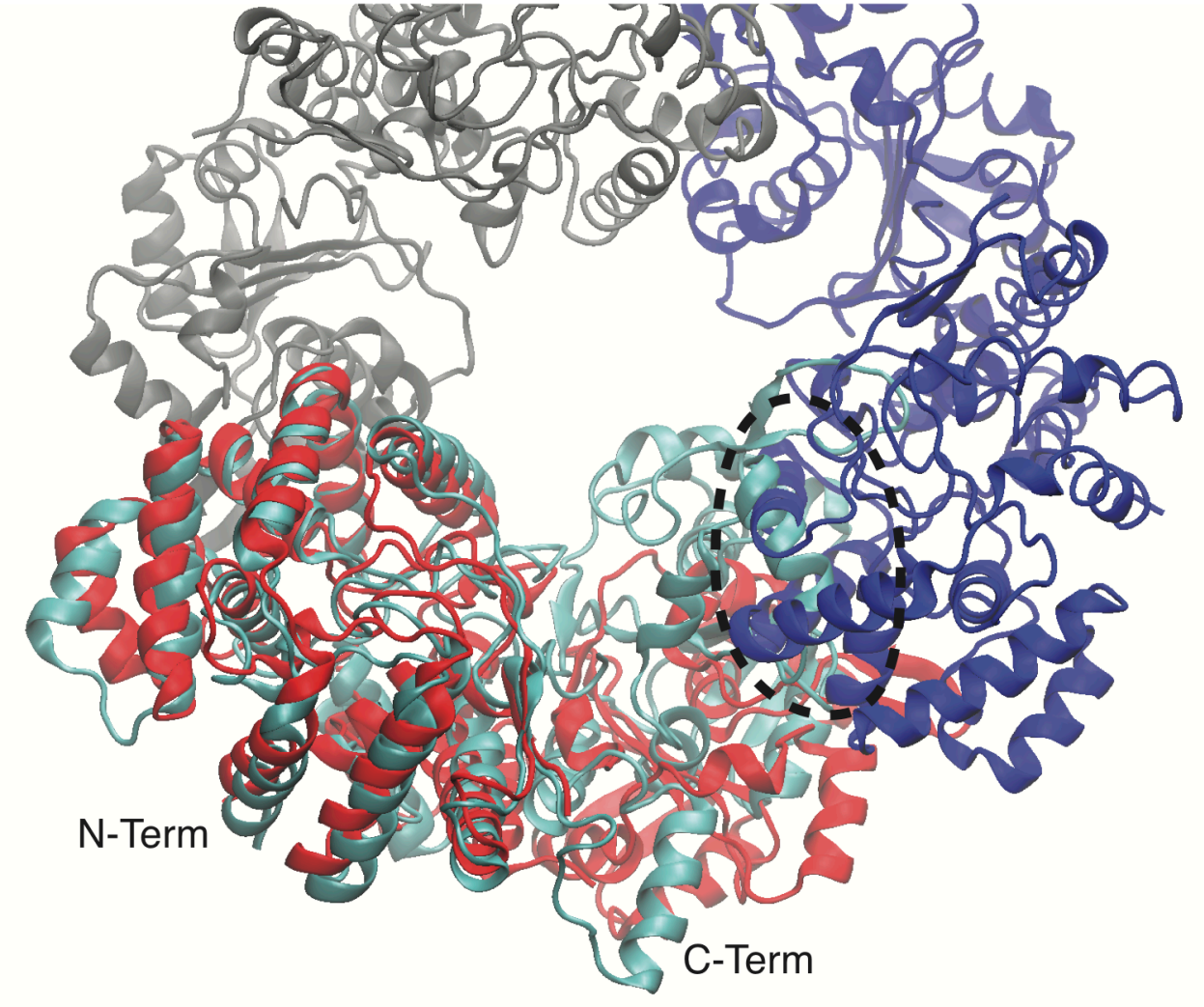


**Figure S4. Relaxed Monomer Structure is Incompatible with Trimer Organization, Related to Figure 3.**

Overlay of the most favorable conformation (F) with a monomer of the trimer (PDBID:3MWP). The most favorable conformation is shown in cyan, while the trimer subunits are colored red, blue and grey. The F structure is aligned on the N-term of the red subunit. The area denoted by the dashed oval shows where the C-term of F would collide with the N-term of the blue monomer, which would prevent the conformational change from occurring.

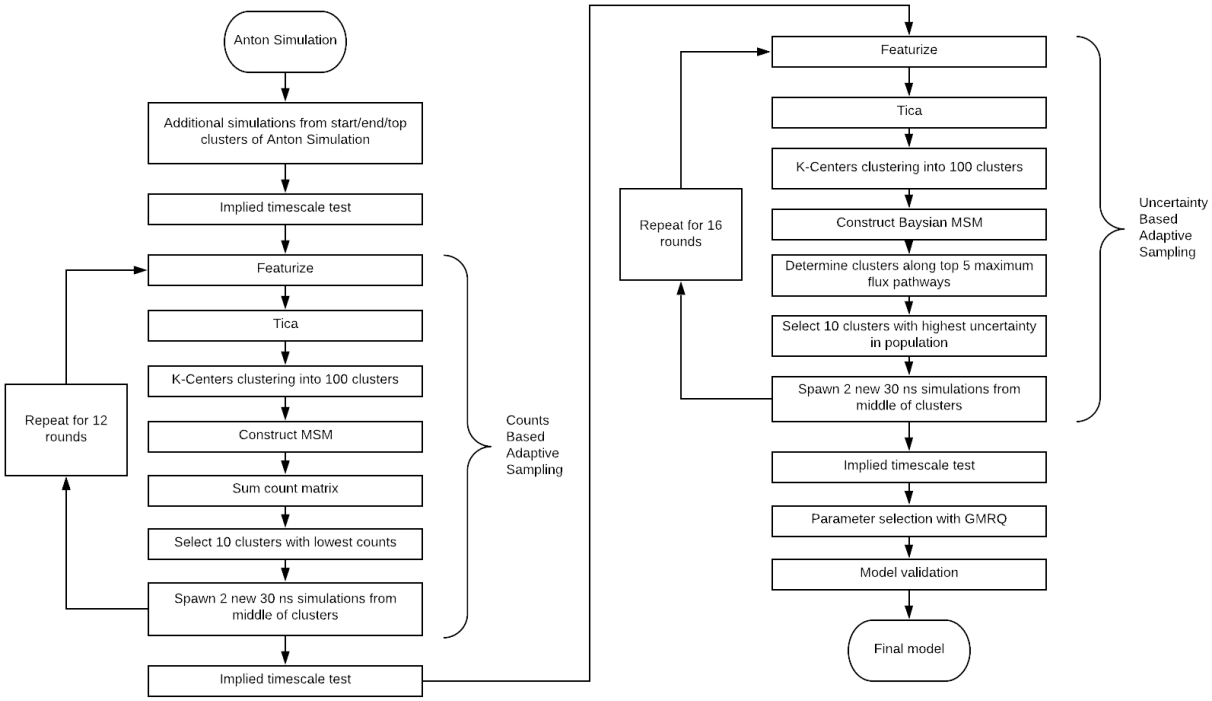


**Figure S5. Workflow Diagram for Adaptive Sampling. Related to STAR Methods.**
Flow chart of the adaptive sampling protocol used in this study.

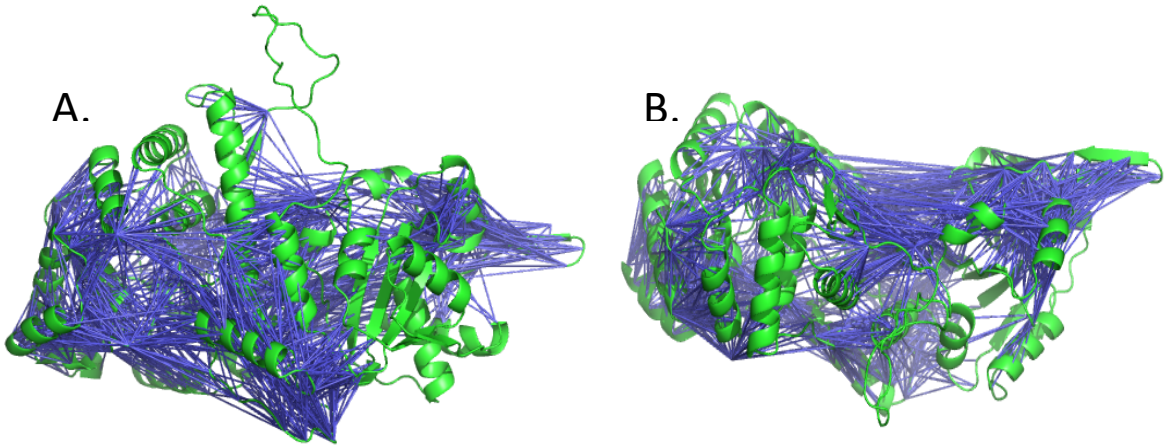


**Figure S6. Contact distances used for features in TICA. Related to STAR Methods.**
Visualization from A) Front and B) Top of 3290 CA distances (shown in blue) used as inputs for TICA. Only distances that are less that 13 Å for at least 2% of the Anton simulation and have a standard deviation greater than 1.5 Å are included. The linker loop is also not included

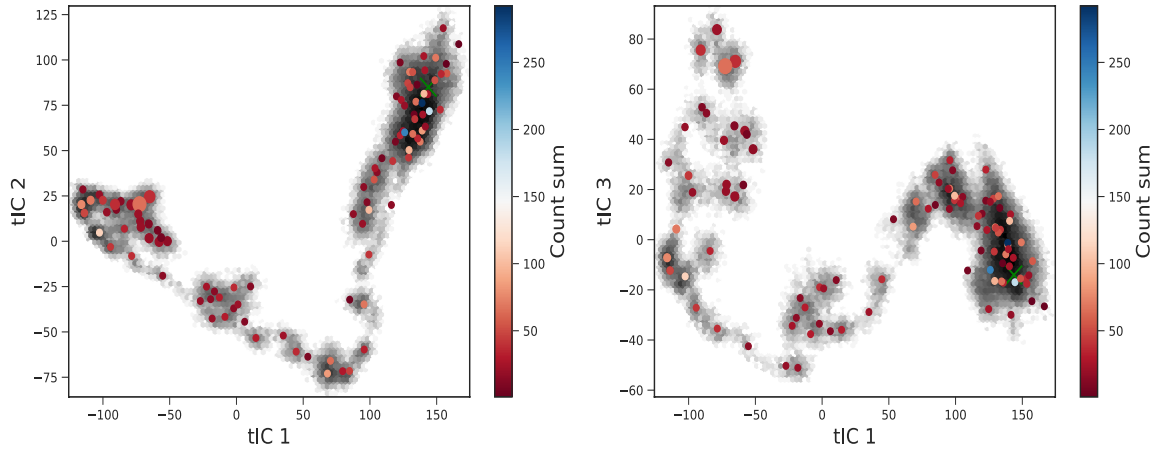


**Figure S7. Counts-based Adaptive Sampling. Related to STAR Methods.** Visualization of round 8 of counts based adaptive sampling. Centers of 100 clusters from k-centers clustering plotted on A) tic 1 vs 2 and B) tic 1 vs 3. Color represents the sum of the row of the count matrix for that cluster. The grey hexbins show a histogram

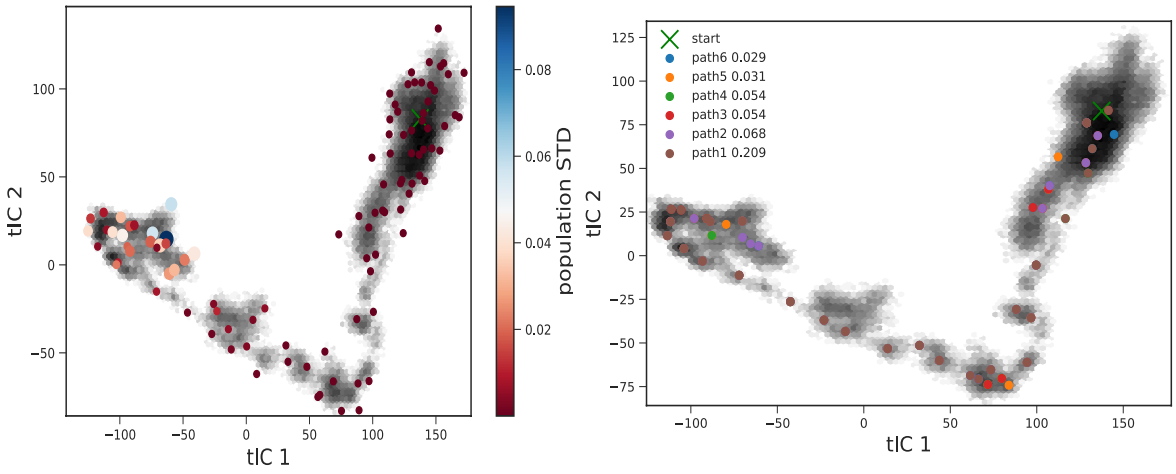


**Figure S8. Uncertainty-based Adaptive Sampling. Related to STAR Methods.** Visualization of round 5 of population uncertainty based adaptive sampling. A) Centers of 100 k-centers clusters are shown on tic 1 vs 2. The color corresponds to the standard deviation in their population from 100,000 transition matrices made using a Bayesian MSM. B) Top 6 maximum flux pathways from the starting structure (green x) to the most populated state. The grey hexbins show a histogram of the raw frames, where darker is a