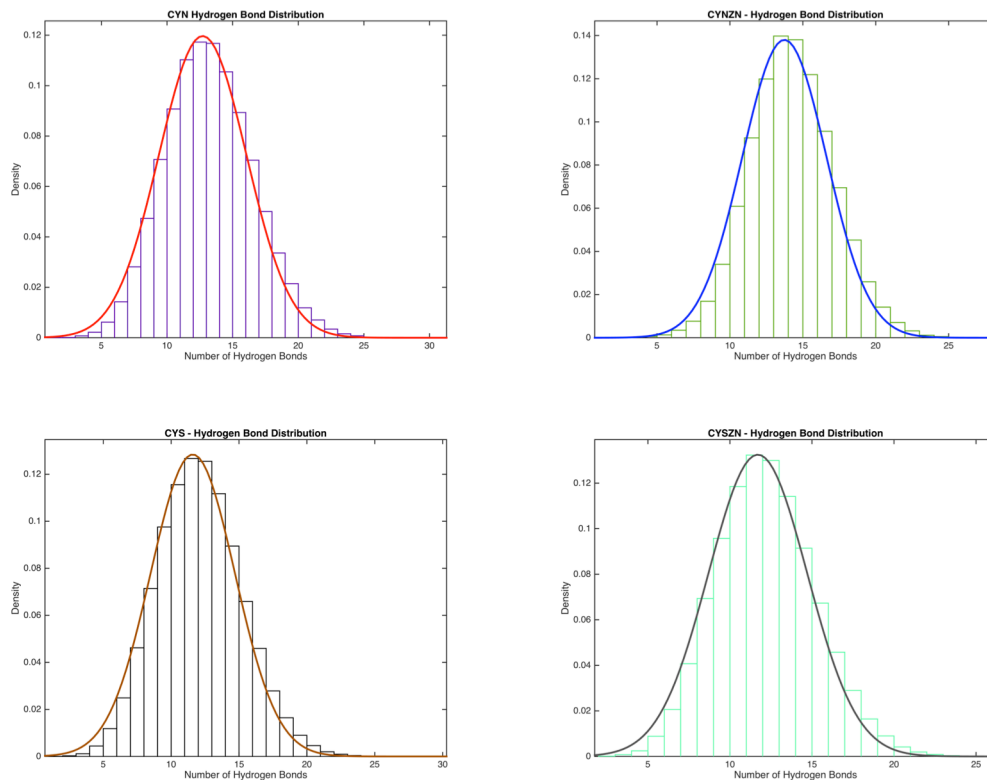
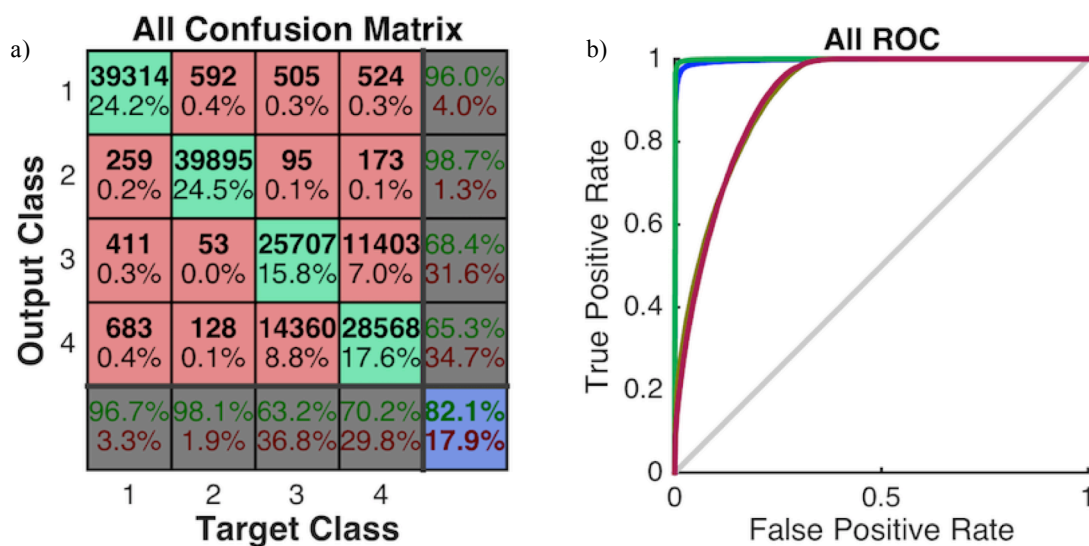


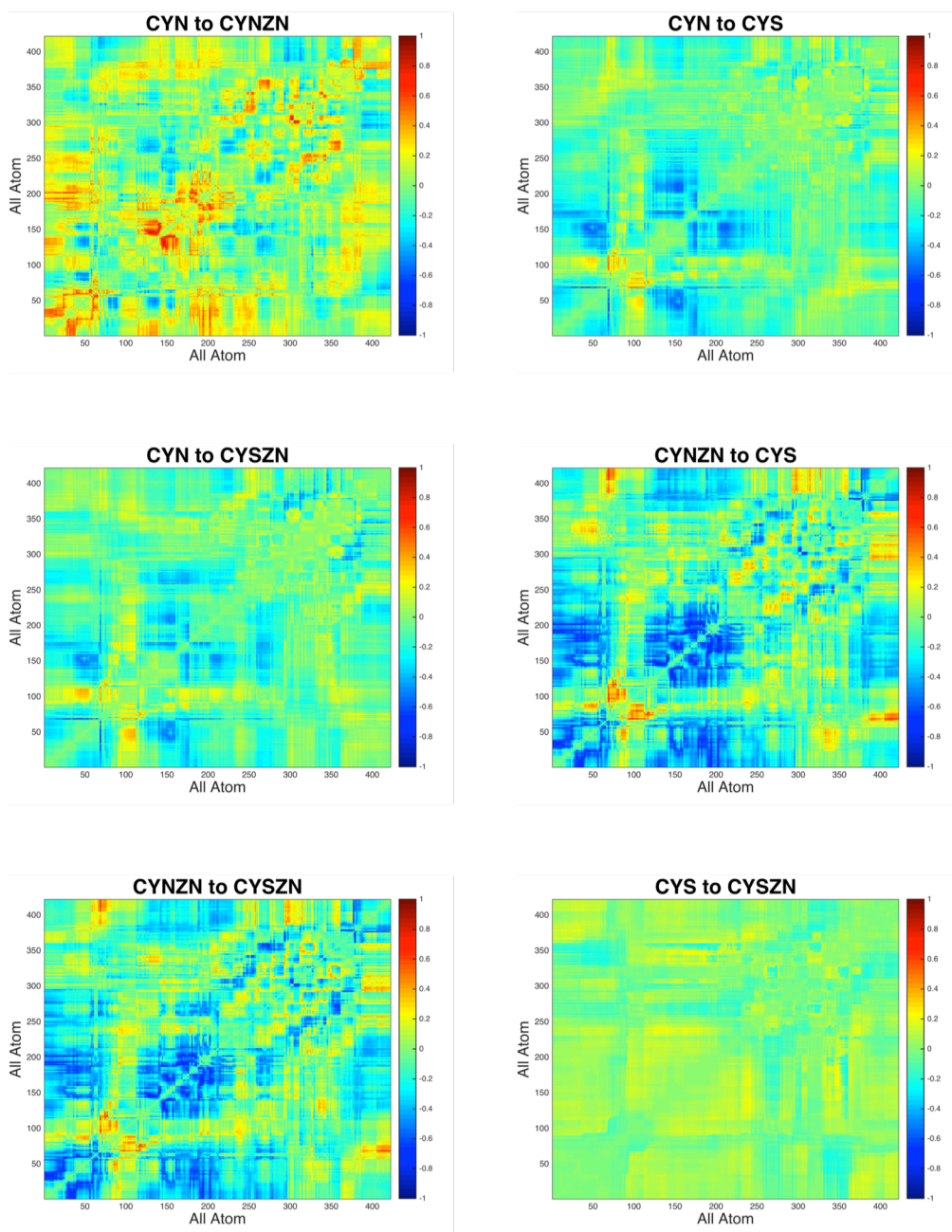
## Supplementary Figures



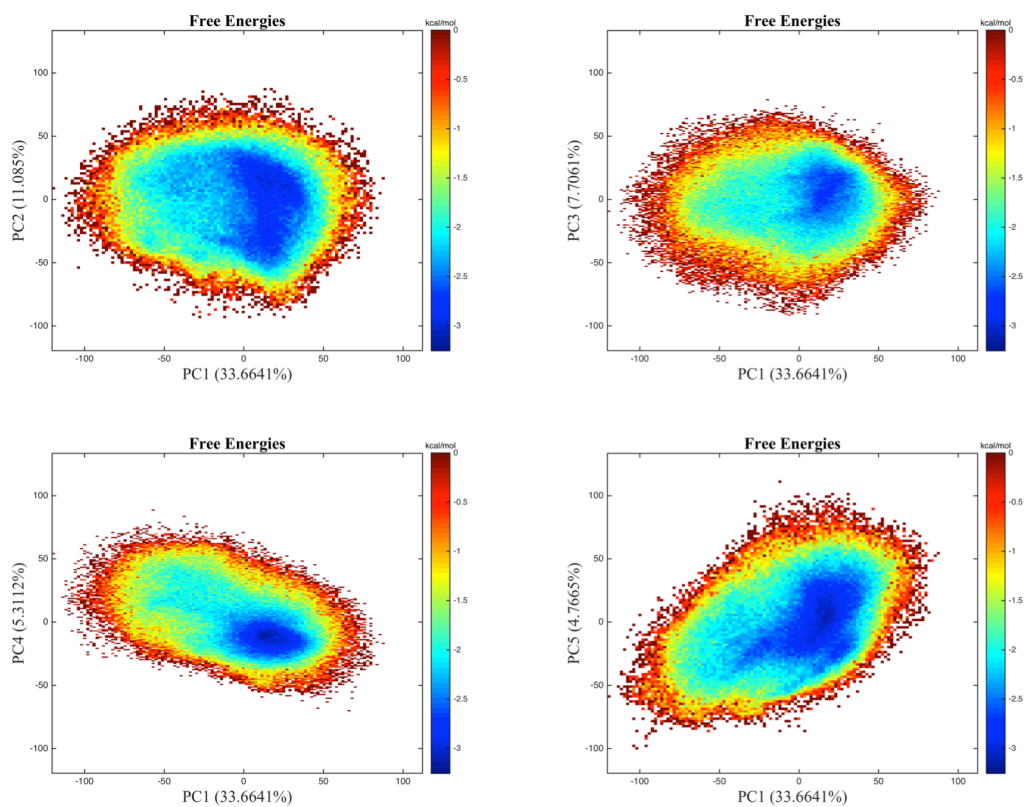
**Supplemental Figure 1.** Histograms of hydrogen bond count distributions of the 4 different configurations throughout each simulation. Fits were performed using the distribution-fitting tool in Matlab™.



**Supplemental Figure 2.** Hydrogen Bond pattern recognition results combine the training, testing, and validation of the pattern recognition toolbox in Matlab as shown via a confusion matrix (a) and ROC curve (b). Pattern recognition readily identifies the deprotonated cases with greater than 96% success, but has a more difficult time differentiating the protonated cases because of the overlap of the hydrogen bond motifs. The trajectory includes 162670 frames of all the configurations concatenated together.

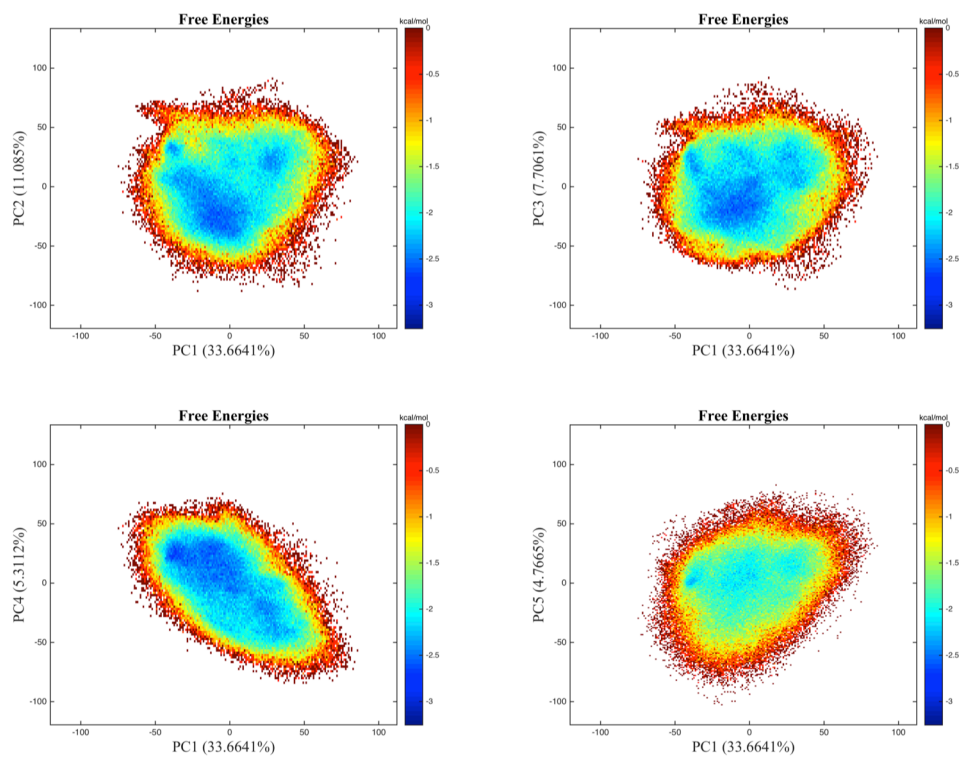


**Supplemental Figure 3.** Subtracted correlations show differences between two correlation matrices to identify regions of similarity and/or dissimilarity between two binding-site configurations. The two protonated cases (CYS, CYS-ZN) are the most similar while the deprotonated, zinc-bound case (CYN-ZN) is the most unique.

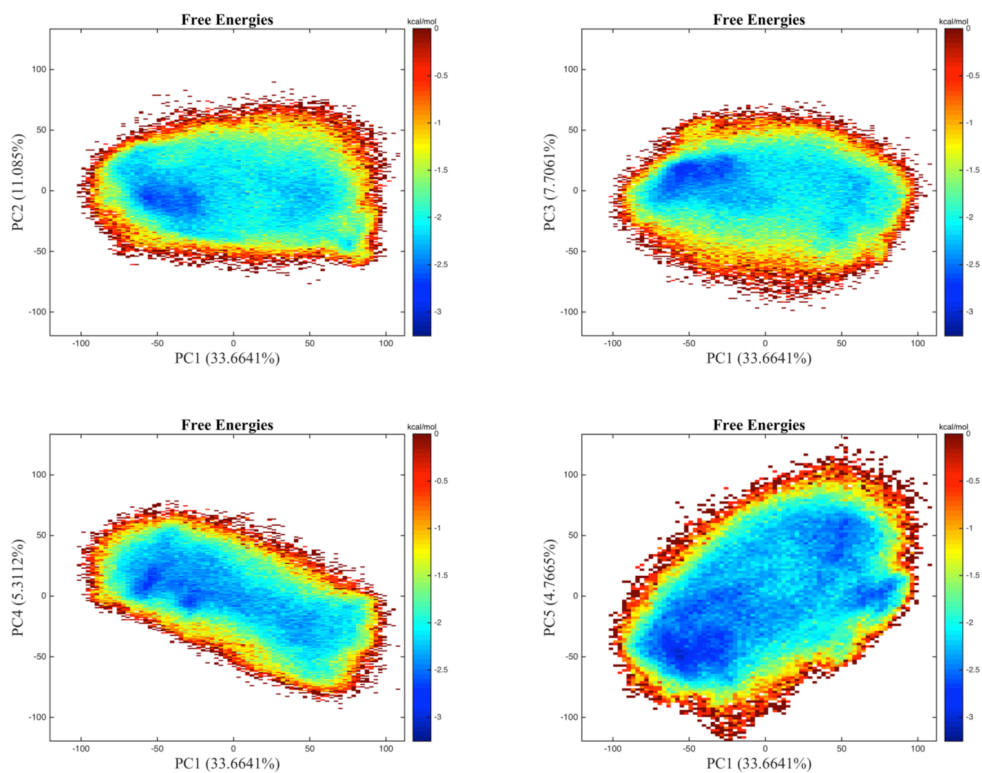


**Supplemental Figure 4a.** PCA Projections CYN showing the projection of the CYN trajectories onto the principal components of CYN-ZN. The wells are broadened in all 4 cases compared to that of CYN-ZN itself, showing greater conformational sampling by the CYN configurations.

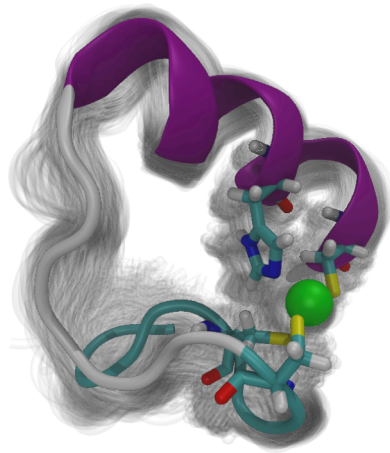




**Supplemental Figure 4b.** PCA Projections CYS showing the projection of CYS onto the principal components of CYN-ZN. The wells are broader than that of CYN-ZN. The distributions are largely uniform consistent with the loss of secondary structure and stabilized fluctuations.



**Supplemental Figure 4c.** PCA Projections CYS-ZN showing the projection of CYS-ZN onto the principal components of CYN-ZN. Once again there is a broadening of the wells compared with CYN-ZN. The distributions are largely uniform consistent with the loss of secondary structure and stabilized fluctuations and the PCA results of CYS.



**Supplemental Figure 5.** The rare but stable configuration of the CYNZN configuration is shown above. Appearing in only 1 of 5 simulations, the conformation dominates the last trajectory. The kinetic trap occupies a unique portion of the PCA plots of the first few WT components. Characterized by the extended turn and perpendicular reorientation of the beta-sheets, this conformation shows unique features currently under further investigation.