



**Figure S3.** Predictions made by the top 9 highest-precision Hybrid Feature Set models according to the voting scheme for thrombin mapped onto the structure of the slow form (1sgi). Each residue in the structure is colored according to a blue->green->red heat map, where the extremes are as follows: red represents residues predicted to be hotspots by 9/9 of the models and blue residues to be predicted hotspots by 0/9 models (predicted non-hotspots by 9/9 models). Experimentally determined hotspots and non-hotspots included in the independent set are rendered in van der Waals spheres (non-hotspots in small van der Waals spheres), along with two additional residues that are part of the allosteric core, Tyr 225 and Tyr184A, but did not meet the criteria for inclusion in the independent data set. For other residues, the prediction is shown along the backbone trace, but no experimental data is available to test the prediction. Correct true positive (hotspot) and true negative (non-hotspot) predictions are colored according to the heat map, while false negatives and false positives are colored gray.