Insights into the Effect of Cross-Linking on Ab Oligomer Formation and Structure SHUTING ZHANG, DILLION M. FOX, BRIGITA URBANC, Department of Physics, Drexel University — Amyloid beta-protein (Ab) is the main component of amyloid plaques thatrepresent one of the hallmarks of Alzheimers disease (AD). Ab forms lowmolecular weight (LMW) oligomers, which are hypothesized to trigger ADpathology. Because of their heterogeneous nature and relatively short life-times, Ab oligomers have not been crystallized to date and consequentlytheir structure has not been experimentally characterized. Covalent cross-linking of Ab oligomers combined with gel electrophoresis can be used tocharacterize oligomer size distributions of two predominant Ab alloforms,Ab40 and Ab42. A recent study reported formation of cross-linked Aboligomers that can form under physiological conditions in the presence ofcopper and hydrogen peroxide. Here, we use efficient discrete moleculardynamics (DMD) combined with the four-bead protein model and aminoacid-specific interactions (DMD4B-HYDRA approach) to examine the ef-fect of cross-linking on Ab oligomer formation. The results of our studydemonstrate that cross-linking via tyrosines facilitates self-assembly of bothalloforms, in particular that of Ab40, yet does not account for the formationof cross-linked Ab40 and Ab42 oligomers larger than trimers and tetramers,respectively. Cross-linking changes the secondary, tertiary, and quaternarystructure of Ab40 and Ab42 dimers and trimers by increasing the exposureof hydrophobic residues and facilitating formation of elongated oligomericshapes that differ from quasi-spherical globular structures observed in con- trol simulations. Our findings imply that amino acids other than tyrosineshave to be involved in cross-linking, the proposition that is currently underinvestigation.

Shuting Zhang
Department of Physics, Drexel University