Contributions of intermolecular and intramolecular amino acid sidechain-sidechain interactions to the structure and stability of amyloid fibrils

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The formation of amyloid fibrils from various proteins and polypeptides is associated with many very serious (and often fatal) human diseases, such as Alzheimer's disease, Creutzfeltdt-Jakob disease, and type II diabetes. An amyloid fiber is composed of beta sheets from various proteins or polypeptides that are stacked along the fiber axis. The aggregation of beta sheets into amyloid fibers generally requires that the beta sheets have complementary structures that allow for efficient stacking. Because of this, the stacking of beta sheets to form amyloid fibers is sequence dependent and the introduction of mutations into the beta sheet structure often results in a failure to form a fibril. This indicates that specific amino acid sidechain-sidechain interactions play a large role in the structure and stability of stacked beta sheet pairs and amyloid fibrils.

In this work we perform dispersion augmented density functional theory (DFT-D) computations on amino acid sidechain-sidechain interactions within an amyloid beta sheet and between pairs of amyloid beta sheets for CA150 (PDB ID 2NNT), an amyloid whose formation is associated with Huntington's disease. Special attention has been given to the treatment of stacking interactions between aromatic residues (phenylalanine, tryptophan, and tyrosine), as it has been suggested that the presence of these strong interactions are critical to amyloid formation.