Abstract Submitted
for the MAR10 Meeting of
The American Physical Society

Dynamics in Alzheimer's disease: the role of peptide flexibility on amyloid beta aggregation MARIA ANTONIETA SANCHEZ FARRAN, JANNA MARANAS, The Pennsylvania State University — Aggregates of the amyloid beta peptide (Aβ) are thought to trigger brain cell death in Alzheimer's patients. Two different types of Aβ aggregates have been identified: soluble, and insoluble. Soluble aggregates are formed in early stages of peptide association, whereas insoluble aggregates are the final state of aggregation. Interestingly, it is the soluble aggregates, not the insoluble ones, which correlate with disease progression. Despite the relevance of soluble aggregates as a target for Alzheimer's disease, their mechanism of formation is unknown. The role of local flexibility in protein function has recently received attention: in this study we ask if local flexibility plays a similar role in how soluble aggregates form. To answer this question, we perform all-atom molecular dynamics simulations of the wild-type Aβ monomer, and two mutated forms that vary in their ability to form soluble aggregates. We find that enhanced flexibility facilitates the formation and availability of nucleation sites by allowing the peptide to more easily access the conformations most favorable to association. Peptides with high flexibility show larger conformational changes than less flexible peptides, the extent of these changes could determine the ability of Aβ to self associate.

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Date submitted: 18 Nov 2009 Electronic form version 1.4