Abstract

Hydrodynamic effect on amyloid-β peptite aggregation

The self-assembly of misfolded amyloid-β (Aβ 1-40/1-42) proteins into insoluble fibrils is strongly linked to the pathogenesis of Alzheimer's disease (AD). The development of new drugs requires the understanding of the mechanisms leading to fibril formation, and the knowledge of the dynamics and structures of the early metastable oligomers which are the main neurotoxic species. Because atomistic simulations in explicit solvent can not be performed on very large systems for a significant time scale, we resort to a coarse grained (CG) protein model with an implicit solvent. Our investigation enlightens the role of hydrodynamic interactions (HI) in the kinetics of β-amyloidogenesis, interactions which are essential, when an implicit solvent is used, to model processes occurring in highly crowded like-cell environments, among others.

Our approach is based on a multi-scale and multi-physics method that couples Lattice Boltzmann and Molecular Dynamics (LBMD) techniques. In our scheme the solvent-mediated interactions are included naturally. As a first step, we focus on Aβ (16-22) peptide, known to form amyloid fibril alone, and we adopt the high resolution CG OPEP (Optimized Potential for Efficient Protein structure prediction) model, developed in our laboratory. For the first time, we have performed quasi-all-atom simulations for very large systems containing thousands of Aβ (16-22) peptides. After the correct tuning of the key parameters of our coupling in order to obtain the experimental diffusivity of Aβ (16-22) monomer and small oligomers, we have demonstrated that HI speed up the aggregation process of medium (100 peptides) and large (1000 peptides) systems.

A detailed characterization of the fluctuating clusters along the trajectories is presented in terms of their sizes and the structural organization of the peptides. Finally, we have investigated how changes in the concentration affect the early aggregation phase of the peptides and their structures.