

Computational studies of structural and electronic properties in Amyloids: from a single chain in solution to crystals

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Amyloid fibrils are a result of protein misfolding, associated with the occurrence of neurodegenerative diseases. These aggregates are rich in beta-sheet domains and interconnected by a network of hydrogen bonds [1]. In some Amyloid fibrils, peculiar optical properties, including absorption of low-energy photons (3.5 eV) and fluorescence in the visible range in the absence of aromatic amino acids has been recently measured [2]. At the same time, the hierarchy in the structure when going from single chain, to protofilament and to fibrils, makes the system challenging under the computational point of view – covering different time and space scales and then requiring several levels of theory. With the aim to provide a multi-scale picture of structural, electronic and optical properties we have:

(a) Performed enhanced sampling classical molecular dynamics of a segment of the amyloid protein A β ₁₋₄₂ in explicit solvent. The conformational landscape of this oligopeptide resembles an intrinsically disordered protein driven by the interplay of polar and hydrophobic interactions and demonstrating the specific role of strong salt-bridges between the N and C termini [3].

(b) Used state-of-the-art ab-initio molecular dynamics simulations of large model systems, to find that in the fibril environment protons can hop along the strong salt-bridges between the N and C termini. The proton transfer events appear to be coupled to subtle changes in the optical properties as gauged by TD-DFT calculations used to characterize the excited states. In addition, we found nuclear quantum effects are likely to play an important role at room temperature [2,4].

References

- [1] Shukla, A. et al., *Arch. Biochem. Biophys.* 2004, **428**, 144-53; Sharpe, S. et al., *Biomacromolecules* 2011, **12**, 1546-55; D. Pinotsi et al. *Chembiochem*, 2013, **14**, 846-50
- [2] D. Pinotsi, L. Grisanti, P. Mahou, R. Gebauer, C. F. Kaminski, A. Hassanali, G. S. Kaminski Schierle, *J. Am. Chem. Soc.*, 2016, **138** (9), 3046–3057
- [3] K. Kwang Hyok, L. Grisanti, and A. Hassanali, *in preparation*
- [4] A. Hassanali, L. Grisanti, D. Pinotsi, C. F. Kaminski, G. S. Kaminski Schierle and R. Gebauer, *in preparation*