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Fiber Diffraction of Amyloid Aggregates Using High brilliance X-ray sources: Opportunities and Challenges

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Protein misfolding and aggregation are central to numerous neurodegenerative diseases [Selkoe, Nature, 2003]. In particular, amyloid-β (Aβ) and α-synuclein are key pathological proteins in Alzheimer's and Parkinson's diseases, respectively. Brain regions where these aggregates accumulate often exhibit high concentrations of metal ions, making it critically important to understand how metal ions influence Aβ and α-synuclein aggregation and fibrillization [Minicozzi, JBC, 2008; Viles, Coord Chem Rev, 2012; De Santis, J Phys Chem B, 2015].

Conventional structural biology methods, such as X-ray crystallography performed at synchrotrons, typically require crystallization steps that can alter native oligomeric or fibrillar states. In contrast, high-brilliance X-ray sources, such as Free Electron Lasers (FELs), generate ultra-intense, femtosecond X-ray pulses, enabling high-resolution imaging of isolated biological samples. This feature makes FELs uniquely suited for investigating structurally heterogeneous systems, including amyloid fibrils and aggregates. Several studies [Laganowsky, Science, 2012; Popp, Cytoskeleton, 2017; Seuring, Nat Commun, 2018] have demonstrated the feasibility of FEL-based diffraction on fiber-like assemblies.

Fiber diffraction provides atomic-level insights into fibril periodicity, while coherent diffraction imaging (CDI) offers complementary information about the size and shape of individual, often non-crystalline aggregates. However, such experiments are technically demanding, with challenges including the intrinsic heterogeneity of the samples, variability in aggregate morphology, and complexities related to hit-finding in serial femtosecond crystallography-type setups. In this presentation, I will discuss both the opportunities and limitations of FELs for the structural characterization of amyloid aggregates.

Primary author: Dr DE SANTIS, Emiliano (Istituto Nazionale di Fisica Nucleare)

Presenter: Dr DE SANTIS, Emiliano (Istituto Nazionale di Fisica Nucleare)

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