Aggregation dynamics in globular proteins: the infrared spectroscopy point of view

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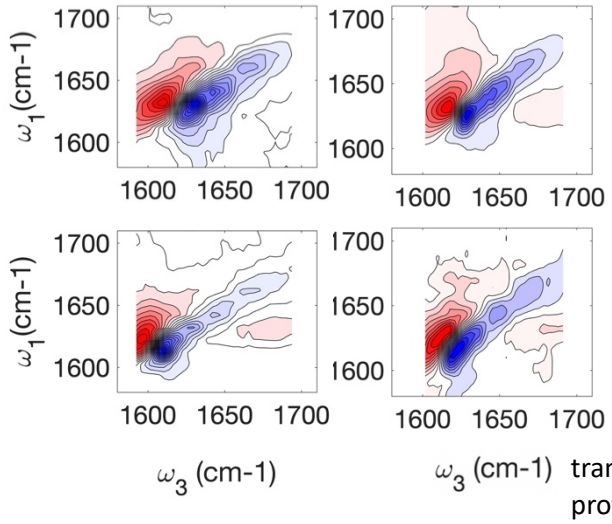
The unfolding and aggregation of globular proteins are central to a wide range of biological and physicochemical phenomena, from pathological amyloid formation in neurodegenerative diseases to the controlled self-assembly of functional biomaterials.[2] Understanding how specific molecular interactions, conformational intermediates, and environmental conditions govern aggregation pathways is therefore crucial both for elucidating disease-related misfolding mechanisms and for harnessing protein aggregation as a design principle for novel, tunable protein-based materials.

Infrared (IR) spectroscopy, especially Fourier Transform IR (FTIR) and advanced 2D-IR, excels at tracking globular protein aggregation by analyzing changes in the **Amide I band (~1650 cm^{-1})**, revealing shifts from native structures (like α-helices) to aggregated forms, primarily **β-sheets**, which form intermolecular bonds and are key to amyloid fibrils. [5]



The thermal and pH-dependent aggregation of selected proteins will be described and how can be followed by using a combination of linear and nonlinear spectroscopies. Distinct intermediate states can be identified under acidic and neutral conditions, revealing different structural intermediates that act as precursors to aggregation. [1] Time-resolved spectroscopic techniques can be employed to deconvolve overlapping spectral features, enabling a detailed analysis of aggregation kinetics and the evolution of intermolecular interactions.[6]
Furthermore, transition dipoles are an underutilized quantity for probing molecular structures. The transition dipole strengths in an extended system like a protein are modulated by the couplings and thus probe the structures. Transition dipole strength (TDS) analysis enhances two-dimensional infrared (2D IR) spectroscopy by probing protein structural differences that frequency alone cannot resolve. The aggregation behavior of mixed protein system can also be examined to probe co-aggregation effects and intermolecular coupling in multicomponent protein systems.[1]

[1] *Venturi, et al. International Journal of Biological Macromolecules 242 (2023) 124621*. *Venturi, et al. Food Hydrocolloids 161 (2025) 110863*

[2] Mezzenga, et al, *Rep. Prog. Phys. 76 (2013) 046601*

[3] *Zanni et al, J. Phys. Chem. B (2015), 119, 14065−14075*. *Buchanan, et all J. Phys. Chem. B (2025), 129, 8360−8367*

[4] *Zanni, et al. J. Phys. Chem. B (2018), 122, 144−153*

[5]Tumbic, et al. Ann. Rev. (2021), 299-321