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Capturing molecular interactions and assembly with a molecular photonic scale

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The cellular processes underpinning life are orchestrated by proteins and the interactions they make with themselves and other biomolecules. A range of techniques has been developed to characterise these associations, operating from the ensemble all the way to the single molecule level. Structural and dynamic heterogeneity, however, continues to pose a fundamental challenge to existing analytical and structural methodologies, despite being key to protein and drug function. I will present recent developments demonstrating that interferometric scattering mass spectrometry (iSCAMS) can mass-image single biomolecules in solution with simultaneous nanometre precision and mass accuracy comparable to native mass spectrometry in the gas phase. As a result, we can resolve oligomeric distributions at high dynamic range, detect small-molecule binding, and quantitatively mass-image not only biomolecules composed of amino acids, but also heterogeneous species such as glyco- and lipoproteins. These capabilities enable us to determine the equilibrium constants and thereby the molecular mechanisms of homo- and hetero-oligomeric protein assembly, which I will illustrate with heat-shock protein oligomerisation and drug-induced HIV glycoprotein cross-linking. Furthermore, by virtue of the intrinsic nanometre spatial precision, we can mass-monitor the dynamics of mesoscopic objects, such as individual amyloidogenic protein aggregates and actin filaments down to the single molecule level. Coupled with clear routes towards future improvements in mass resolution and precision well below the kDa range and extension towards membrane proteins, these results illustrate how single molecule mass imaging provides universally-applicable and spatially-resolved access to the mechanisms and dynamics of protein assemblies, their interactions and how they form nano- and mesoscopic structures, one molecule at a time.

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