

Ewelina Lipiec⁽¹⁾

E. Lipiec^{(a),*}, A. Chahaj-Brekiesz^(b), M. Czaja^(a,c), J. Kaderli^(d), J. Kobierski^(e), D. Lupa^(a), D. Perez-Guaita^(f), S. Seweryn^(a,c), K. Skirlińska-Nosek^(a,c), K. Sofińska^(a), M. Szymoński^(a), A. Wnętrzak^(b), B. Wood^(f), R. Zenobi^(g)

^(a) Jagiellonian University, Faculty of Physics, Astronomy and Applied Computer Science, M. Smoluchowski Institute of Physics, Łojasiewicza 11, 30-348 Krakow, Poland,

^(b) Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, 30-387 Kraków, Poland

^(c) Jagiellonian University, Doctoral School of Exact and Natural Sciences, Krakow, Poland

^(d) Laboratory of Physical Chemistry, 8093 Zürich, Switzerland,

^(e) Faculty of Pharmacy, Jagiellonian University Medical College, 31-007 Kraków, Poland

^(f) Centre for Biospectroscopy and School of Chemistry, Monash University 3800, Victoria, Australina

^(g) Department of Chemistry and Applied Biosciences, ETH Zurich, 8093 Zurich, Switzerland

Contact@E-mail Ewelina.Lipiec@uj.edu.pl

Mind the gap! Plasmonic nanocavity for trapping of local molecular rearrangements in selected biomolecules

Despite decades of intensive research, the fundamental molecules of life, including nucleic acids, proteins, and lipids continue to reveal new and poorly understood aspects of their structure and function. One of the major challenges is the limited sensitivity and spatial resolution of conventional analytical techniques, which makes it difficult to investigate the pronounced nanoscale heterogeneity of these biomolecules and fully understand how their local properties determine their functionality.

A deeper understanding of the molecules of life therefore requires advances in molecular nanospectroscopy, together with a detailed understanding of the physical and chemical processes taking place within plasmonic nanogap junctions. In particular, it is essential to elucidate the generation of surface plasmons, the confinement of electromagnetic fields within nanoscale junctions and cavities, and the resulting enhancement of optical fields in the immediate vicinity of the molecules under investigation. These enhanced fields can significantly increase molecular vibrational excitations and Raman scattering, forming the physical basis of advanced techniques such as Tip-Enhanced Raman Spectroscopy (TERS).

Our research has focused on applying nanospectroscopy to investigate the local secondary structure of proteins and peptides associated with Alzheimer's disease during their aggregation. By mapping the nanoscale distribution of β -sheet structures, we were able to follow the aggregation pathways of amyloid- β and tau proteins [1]. We also performed pioneering TERS measurements of amyloid- β under liquid conditions, demonstrating that the solvent environment can improve the quality of the spectroscopic data while providing additional protection for the biomolecules [2]. TERS measurements further enabled us to monitor local molecular rearrangements occurring during the pathological fibrillation of tau protein [3,4].

Because lipids can influence the secondary structure and aggregation behaviour of amyloid proteins, we also investigated lipid monolayers using AFM-TERS and STM-TERS. These approaches provide nanoscale information on the local molecular distribution and orientation, as well as phase separation and domain formation within lipid layers [5]. In parallel, our research addresses the chemical structure of DNA and conformational changes associated with the transition from B-form to A-form DNA [6,7]. Together, these studies demonstrate the potential of TERS to reveal molecular structure and dynamics at spatial scales that are inaccessible to conventional spectroscopic methods.

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