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Shedding light on glucose

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Abstract: Non-invasive glucose monitoring remains a key challenge due to the molecule's inherently weak Raman signal. While surface-enhanced Raman spectroscopy (SERS) offers potential, it often suffers from incomplete spectral coverage. A recent work using tip-enhanced Raman scattering (TERS) successfully captures glucose's complete vibrational fingerprint. This label-free approach paves the way for highly sensitive metabolite detection and future in vivo biosensing applications.

Keywords: non-invasive glucose monitoring; Raman spectroscopy; tip-enhanced Raman scattering (TERS); metabolite detection; biosensing

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Glucose, meaning "sweet" in Greek, is the primary source of energy, essential for keeping every single cell in our body functioning, ranging from red blood cells to brain cells. Therefore, any imbalance in the level of Glucose in our blood can cause many diseases, predominantly diabetes. As a result, accurate detection of glucose molecules is crucial for diagnostics, disease monitoring, or medical care[1].

Today, finger pricks are the most commonly used detectors for measuring blood glucose levels. However, the painful procedure has made it very unpopular among patients, particularly those. Therefore, developing non-invasive glucose measurement techniques has become an increasingly sought-after goal in numerous scientific and technological communities, including those in the fields of microwave, acoustic, and optical technologies. Among these fields, optical techniques such as near-infrared and Raman spectroscopy have demonstrated very promising approaches[2–5]. While near-infrared spectroscopy detects glucose molecules that absorb specific wavelengths, Raman spectroscopy analyses the light deflected by glucose molecules. Therefore, Raman spectroscopy can analyse water-containing samples, while the near-infrared technique is hindered by water absorption[2–5]. Hence, Raman spectroscopy has gained a remarkable reputation as a powerful, label-free approach to identify numerous molecules, such as proteins, nucleic acids, lipids, etc, through their unique vibrational fingerprints[6].

Despite the high potential of the Raman spectroscopy technique, it has long struggled to provide reliable molecular insights into Glucose, due to Glucose's inherently weak Raman scattering cross-section, which is nearly five times smaller than that of Benzene, and its poor affinity for bare metal surfaces[2]. While surface-enhanced Raman scattering (SERS) can theoretically amplify these weak signals, incomplete spectral coverage and interference from linker molecules continue to hinder reliable and comprehensive analysis. Overcoming these barriers for Glucose detection has remained a long-standing challenge.

In a recent article published in *Opto-Electronic Science*, Xie Z et al. demonstrate the power of tip-enhanced Raman scattering (TERS) to record the complete vibrational spectrum of glucose molecules within the Raman recording window 400–3200 cm^{-1} range[7]. The tip concentrates a strong longitudinal electric field along its axis, maximising the localised hotspot at the apex. This boosts near-field enhancement, enabling more complete vibrational fingerprints to be captured and increasing Raman signal intensity. As illustrated in Fig. 1, by combining a shear-force feedback-controlled scanning probe with a radially polarised vector beam launched through an optical fibre tip, the authors achieve both strong near-field confinement and far-field background suppression. This carefully engineered

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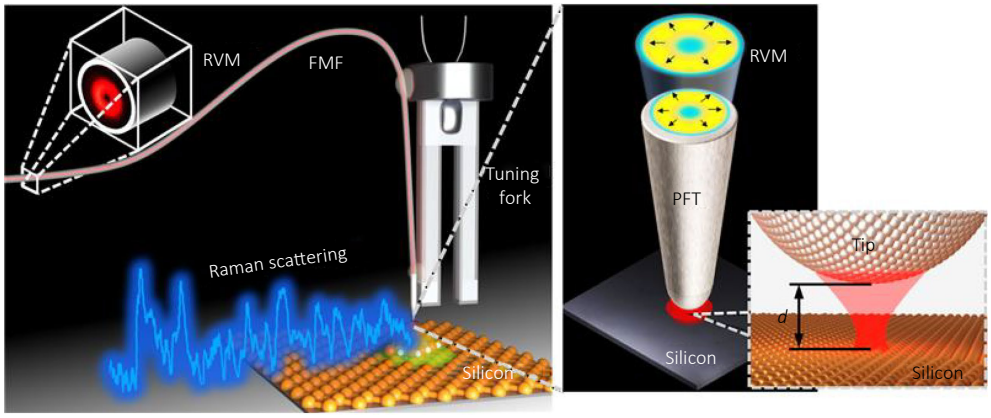

Fig. 1 | The schematic illustration of the tip-enhanced Raman scattering platform integrated with shear-force feedback of the scanning near-field microscopy. Figure reproduced with permission from ref.[7], under a Creative Commons Attribution License.

configuration enables direct observation of all Glucose vibrational modes with exceptional clarity.

Capturing the full vibrational modes' spectrum of Glucose not only validates the potential of TERS for equipping Raman Spectroscopy to measure Glucose but also paves the way for studying other metabolites and saccharides that have remained spectroscopically elusive. Importantly, the comprehensive spectral information can allow for the differentiation of subtle conformations and isomers, opening up new possibilities for molecular-level biochemical analysis.

In summary, extending the TERS platform, proposed in this paper[7], to aqueous and biological environments could be the missing link for developing non-invasive, label-free glucose sensors. Moreover, merging this technique with other ongoing advances in the field, such as developing advanced structured tip designs or exploiting artificial intelligence for data analysis, has a strong potential to revolutionise in vivo diagnostics techniques for measuring many molecules beyond Glocouse.

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