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SORS and SESORS: deep Raman spectroscopy in biomedical analysis and disease diagnosis

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Spatially offset Raman spectroscopy (SORS) and its surface-enhanced variant, SESORS, have emerged as transformative techniques in analytical chemistry and biomedical diagnostics, enabling non-invasive, depth-resolved molecular sensing. SORS facilitates the probing of endogenous signals from subsurface layers, while SESORS enhances sensitivity through plasmonic nanostructures, allowing sensitive targeted detection of exogenous diagnostic agents. Spatially offset Raman spectroscopy is now making significant strides in clinical diagnostics. This review focuses on the rapid advancements in the field over the past five years, including applications in cancer diagnosis, monitoring of therapeutic response, bone health assessment, and tracking of neurotransmitters and SERS-labelled nanoparticles through tissue depths exceeding 7 cm in a tissue wrapped mouse model and 14 cm from within a porcine tissue stack. The integration of tailored nanostructures, resonant Raman labels, and advanced optical instrumentation has expanded the versatility of SESORS, with modalities such as transmission, backscattered, and resonance-enhanced configurations offering flexibility across diverse clinical scenarios. Despite challenges in standardisation, biocompatibility, and instrumentation, interdisciplinary progress in optics, nanotechnology, and spectroscopy continues to drive innovation. This review critically examines the recent evolution, classification, and biomedical applications of SORS and SESORS, highlighting their limitations and future potential in translational medical research.

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1. Introduction

A wide range of biomedical and clinical applications necessitate non-invasive, depth-resolved molecular sensing for *in vivo* analysis. Among these, cancer diagnosis remains a critical area, where disease onset and progression are often accompanied by subtle yet significant biochemical alterations within cells and tissues. Conventional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound have long served as the cornerstone of clinical diagnostics. CT, MRI, PET, and ultrasound each play important and complementary roles in clinical imaging.[1,2] CT is fast and widely available for anatomical assessment but offers limited molecular contrast and uses ionizing radiation. MRI provides excellent soft-tissue and functional information without radiation, though it is relatively costly, time-intensive, and does not usually provide direct biochemical specificity. PET is a central molecular imaging modality with high sensitivity, supported by targeted radiotracers and radiotheranostic agents such as ^{68}Ga-PSMA and $_{18}$F-PSMA.[3] Ultrasound is accessible, real-time, and cost-effective, although its routine biochemical specificity remains limited. Fluorescence-guided imaging agents such as pafolacianine (Cytalux) further show that high molecular specificity can be achieved clinically.[4,5] All of the above modalities generally lack the direct native biomolecule detection capability required for early-stage disease detection, therapeutic monitoring, and biochemical characterisation of tissue microenvironments.

By contrast, Raman spectroscopy provides direct biochemical readouts through molecular vibrational fingerprints. In its deep-tissue forms, Raman offers a dual capability: label-free interrogation of intrinsic biomolecular composition and, when combined with nanoparticle tags, sensitive tracking of labelled targets. This progress has been significantly accelerated by the development of spatially offset Raman spectroscopy (SORS), which enables the interrogation of subsurface layers by spatially separating the excitation and collection zones on sample surface.[6] The subsequent integration of SORS with surface enhanced Raman spectroscopy (SERS) has led to the advent of surface enhanced spatially offset Raman spectroscopy (SESORS),[7,8] a hybrid technique that combines depth sensitivity with signal amplification *via* plasmonic nanostructures. With various forms of SORS often employed with SERS nanostructures, a generalized term of deep Raman or offset Raman as an umbrella for different types of methods has been used in the literature.[9–11]

SORS enables subsurface biochemical analysis through diffusely scattering tissue, while SESORS combines depth access with signal enhancement and molecular targeting for detection of labelled nanoparticles at otherwise inaccessible depths. Raman, SORS, and SESORS should therefore be viewed not as replacements for established imaging modalities, but as complementary approaches that can add chemically specific and microenvironment-relevant information alongside anatomical, functional, and molecular imaging. The ability to retrieve molecular information from depth is of paramount importance in biomedical diagnostics. Many pathological processes, including tumour development, inflammation, and metabolic disorders, originate or manifest within deeper tissue layers. Surface-level analysis may fail to capture these changes, leading to delayed or inaccurate diagnoses. Moreover, the biochemical composition of tissues at depth often differs from that of superficial layers due to gradients in oxygenation, pH, and cellular heterogeneity, within tissue layers, but also at greater depths, depending on anatomical locations, entirely different tissues can be found. Techniques such as SESORS allow researchers and clinicians to access these hidden molecular signatures, enabling early detection, precise localisation, and real-time monitoring of disease progression and therapeutic response.

SESORS has demonstrated the capability to probe through tissue depths up to 14 cm,[12] making it suitable for analysing anatomical regions at the extremities, such as limbs, breast, and potentially brain. However, if light is injected within the body using fibre optics any organ would be potentially accessible this way.[13] This has opened new avenues for non-invasive cancer diagnosis, bone health assessment, and neurochemical sensing. The integration of tailored nanostructures, resonant Raman labels, and advanced optical instrumentation has further expanded the versatility of SESORS, with modalities such as transmission, backscattered, and resonance-enhanced configurations offering flexibility across diverse clinical scenarios.

This review provides a comprehensive overview of the recent advances in SORS and SESORS (including both SERS + SORS and SERS + Transmission Raman Spectroscopy (TRS)), with a particular focus on developments over the past five years. It builds upon earlier foundational work and highlights emerging applications in cancer diagnostics, therapeutic monitoring, and molecular imaging. The review also critically examines the evolution of Raman instrumentation, the design of SORS probes, SERS-active nanostructures, and the refinement of

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Raman labels, while evaluating the limitations and translational challenges associated with clinical implementation. Through this lens, the article aims to elucidate the growing impact of SORS and SESORS in biomedical research and their potential to transform non-invasive diagnostics and personalised medicine.

SORS techniques

SORS utilises the inherent properties of photon diffusion, which have also been exploited in an analogous manner with other techniques such as NIR and fluorescence for deep sensing inside turbid media.[6,14,15] SORS brings in high chemical specificity making it particularly well suited for detecting subtle chemical alternations in complex turbid matrixes such as biological tissues. In SORS,[6,14] the key differentiating feature from conventional backscattering Raman is the separation of the Raman collection region on the sample surface from the laser illumination area – their separation termed spatial offset. The larger the spatial offset the larger the probing bias towards deeper zones inside the sample. With a layered sample, a commonly encountered situation in biology, the variation of the spatial offset leads to varying relative content of Raman signal detected from individual layers. Therefore, acquiring signal at different spatial offsets can be used to isolate Raman signatures of individual layers through mathematical processing – in essence scaled subtractions of individual spectra from each other.[6,14] Alternatively, multivariate analysis can also be used to isolate spectra of individual layers.[6]

SORS can be deployed with different illumination and collection geometries. The basic one is a point-like illumination and collection geometry (see Fig. 1A). A more effective approach can be a circle collection pattern with a point like illumination at its centre. A reverse of this geometry, inverse SORS, where the laser illumination zone is shaped in a ring pattern and Raman signal is collected from the centre of the ring with the radius of the illumination ring facilitates the spatial offset has a particularly important role in biomedical applications.[16–18] This is because a larger ring radius and consequently increased associated area permits the use of increased laser power, benefitting *in vivo* applications where intensity limits often need to be adhered to for safety reasons. Such ring-shaped laser beams can be readily produced using a conical lens ('axicon').[19] Alternatively light modulation devices can be used to generate desirable illumination and collection patterns.[20] As noted earlier the size of the spatial offset determines the probed depths. This has been the subject of a recent systematic study providing guidance on how deep SORS is sensing.[21,22] The setting of optimum spatial offset was also investigated by Maher and Berger.[19] The laser light and collected Raman signal can be coupled to and from the sample using optical fibres or free space optics.[23]

SORS is restricted in situations where significant absorption occurs, at either the laser or Raman wavelengths, obstructing photon diffusion process leading to reduced probed depth. With biomedical samples this issue can often be circumvented with NIR laser excitation wavelengths,[11,18,25] where minimum absorption is present with most biological tissues. Other limitations include potential interference from fluorescence, where present at excessive levels, overwhelming the detected Raman signal. This is more of an issue of fluorescence originating from the target layer, as fluorescence from superficial layers can often be effectively supressed by introducing spatial offset,

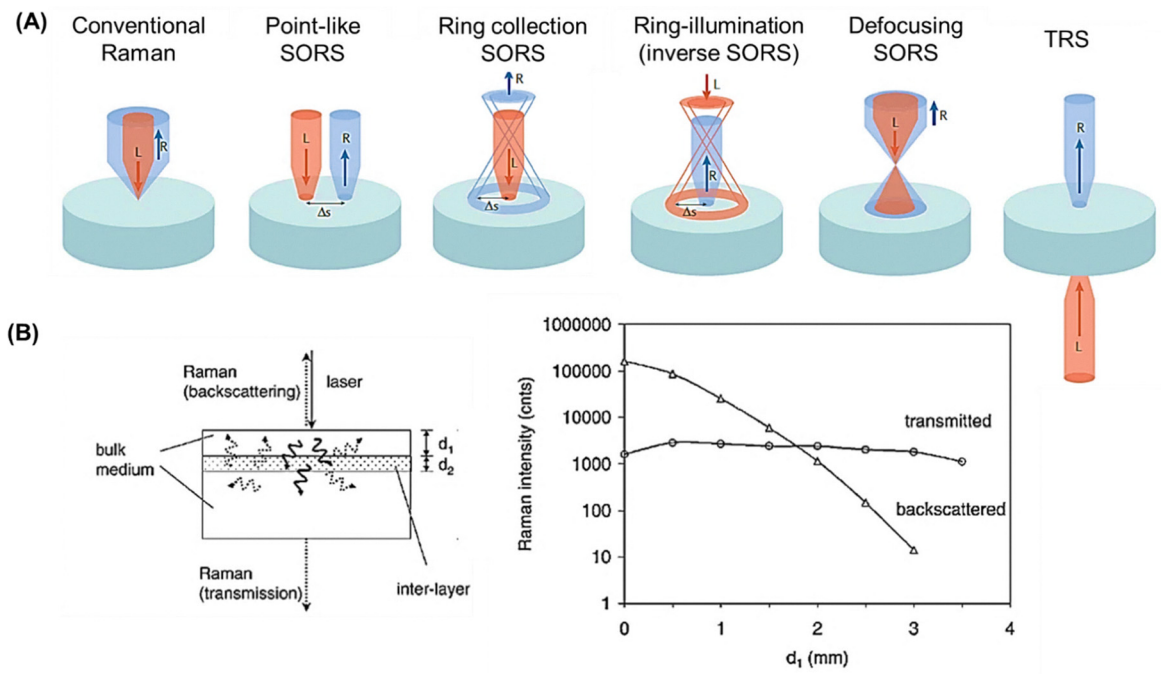

Fig. 1 (A) SORS illumination and collection geometries,[9] and (B) comparison of transmission and backscattered SORS signal intensities.[24] Fig. 1A, adapted with permission from [Springer Nature Limited],[9] copyright 2012. Fig. 1B, adapted with permission from [Sage Publications],[24] copyright 2006.

in the same way as Raman signal is suppressed from these layers.[14]

A related sampling geometry, that is also highly relevant for biomedical applications, is transmission Raman spectroscopy (TRS).[9] In this configuration, the laser illumination and Raman collection areas are positioned on opposite sides of the sample. TRS can therefore be viewed as a special case of SORS in which the spatial separation between illumination and collection is taken to an extreme. Unlike conventional backscattered SORS, which can be tuned to preferentially sample subsurface layers at selected depths, TRS generally produces signals that are more representative of the average composition across the full interrogated volume, although some bias toward central or front/back regions may still occur depending on the exact optical properties and measurement and sample geometry. As such, TRS provides an approximate volumetric readout of the probed tissue rather than depth-selective information.[8,26] This makes TRS particularly useful when the target is expected to be distributed within a larger tissue volume, or when the exact depth of the target is not known in advance. In such cases, the volumetric nature of TRS can be advantageous because it increases the likelihood of capturing diagnostically relevant subsurface signals without requiring precise prior depth localization. Fig. 1B illustrates the signal intensity trends observed with TRS and backscattered conventional Raman across a range of target layer depths.[24] It shows that backscattered Raman is strongly biased to near surface areas, whereas TRS provides more uniform signal strength with target layer depth. This property is especially valuable in applications such as the detection of breast calcifications, where the target may be embedded within heterogeneous tissue and its precise depth may not be known beforehand.

2. SORS in biomedical analysis and disease diagnosis

Spatially offset Raman spectroscopy has emerged as a transformative analytical modality in biomedical science, enabling non-invasive access to chemically specific information from subsurface layers of biological tissue. Its depth-resolving capabilities have facilitated applications ranging from pharmaceutical authentication to *in vivo* disease diagnostics.

Enhancing Raman signal acquisition from subsurface layers

Optimising the Raman signal from subsurface tissue layers is a critical aspect of SORS, particularly in biomedical applications where signal attenuation and noise can significantly affect diagnostic accuracy. A key determinant of signal quality is the selection of appropriate spatial offsets, which must be tailored to sample geometry and its optical properties. Both theoretical modelling and empirical experimentation are employed to identify optimal offsets. Typically, an increase in spatial offset correlates with deeper tissue interrogation; however, this is accompanied by a concomitant reduction in signal intensity due to photon diffusion and absorption.

Numerical approaches, such as photon migration simulations, have been utilised to predict the signal-to-noise (S/N) ratio at varying offsets. These methods require detailed knowledge of the sample's scattering and absorption coefficients, and while informative, they are less commonly applied due to their computational complexity. Maher and Berger[19] have systematically investigated the relationship between spatial offset and acquisition time, emphasising that larger offsets necessitate extended integration periods to maintain acceptable S/N ratios.

As a trade-off exists: while larger spatial offsets enable deeper probing, they also diminish the Raman signal strength. Achieving an optimal balance between depth sensitivity and spectral quality is often achieved empirically by iterative adjustments of experimental parameters, including laser power, acquisition time, and detector sensitivity. Such optimisation remains the most practical approach in clinical settings, where tissue heterogeneity and patient-specific variables complicate predictive modelling.

To maximise signal recovery from depth, several instrumental and procedural considerations must be addressed. These include the estimation of optimal spatial offsets based on tissue type, the use of appropriate laser powers to ensure patient safety, and the deployment of spectrographs with high quantum efficiency in the near-infrared (NIR) region and low thermal and readout noise. Furthermore, the configuration of the SORS system, whether employing concentric ring collection geometries, linear arrays, or transmission-based setups, plays a pivotal role in enhancing depth-resolved signal acquisition.

Through-container quality assessment of medicinal and healthcare products

SORS has been employed for the discrimination between genuine and falsified COVID-19 vaccines,[27] as illustrated in Fig. 2A, and for the longitudinal monitoring of blood quality in sealed storage bags.[28] Beyond these examples, SORS is increasingly being explored as a practical through-container screening tool for other medicinal products too where non-destructive analysis, rapid deployment, and preservation of sterility are important. Recent work[29] has shown that handheld SORS can detect toxic contaminants such as ethylene glycol (EG) and diethylene glycol (DEG) in medicinal syrups within closed containers, with detection limits of around 0.5% in neat propylene glycol, around 1% in neat glycerol, and around 1–5% in marketed syrup formulations depending on formulation composition. The study further notes that, although this does not reach the 0.1% pharmacopeial threshold required for purity checks, the method is still valuable for identifying gross substitution, major contamination events, raw-material mislabelling, in supply-chain screening in field settings. SORS has also been used for the quantitative analysis of hand sanitizers directly through commercial packaging, extending its utility to sealed healthcare and consumer health formulations.[30] Taken together, these studies demonstrate that SORS is well suited to situations in which medicinal contents must be assessed through opaque or strongly scattering containers,

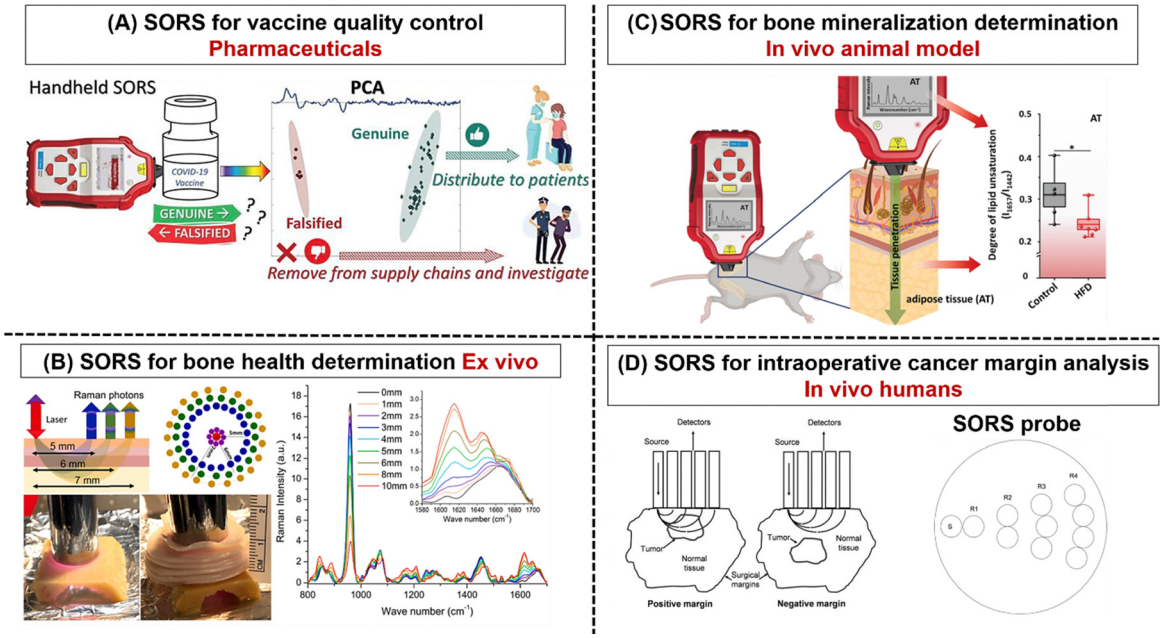

Fig. 2 SORS biomedical applications for (A) vaccine quality determination,[27] (B) bone health determination,[31] (C) *in vivo* SORS for bone mineralization determination,[32] (D) intraoperative cancer margin of 1–2 mm detection.[33] Fig. 2A, adapted with permission from [Elsevier B.V.],[27] copyright CC-BY 4.0 2023. Fig. 2B, adapted with permission from [Elsevier B.V.],[31] copyright 2023. Fig. 2C, adapted with permission from [American Chemical Society],[32] copyright CC-BY 4.0 2024. Fig. 2D [left panel], adapted with permission from [SPIE],[33] copyright 2011.

making it attractive for pharmaceutical authentication, contaminant screening and broader point-of-need quality assurance.

Bone quality assessment

SORS has shown considerable promise in the non-invasive evaluation of bone integrity, with implications for diagnosing osteoporosis, and bone malignancies. Researchers have demonstrated the ability of SORS to isolate pure bone spectra from human fingers, suppressing surface tissue interference. Sowoidnich *et al.*[34] investigated photon migration through bones of varying mineralisation, including equine metacarpal, deer antler, and whale tympanic bulla, and demonstrated Raman signal recovery through up to 4.7 mm of cortical bone. These findings inform optimal spatial offsets for diagnostic applications and highlight the influence of mineral density and porosity on photon migration. Recent studies highlight the growing value of SORS for non-invasive bone assessment, particularly in applications related to bone ageing,[35] osteoporosis,[36] and joint health. Longitudinal work in mice has shown that label-free SORS can track age-related changes in bone composition over time, supporting its potential as a transcutaneous tool for monitoring skeletal health. Related cadaveric studies, on excised human finger bones, further suggest that SORS measurements at peripheral skeletal sites may carry clinically relevant information for predicting conditions such as wrist osteoporosis.[36] Beyond bone alone, SORS has also been extended to cartilage and osteoarthritis assessment, where offset Raman collection enables access to chemically informative subsurface cartilage layers beneath overlying tissue.[37] Together, these studies position SORS as a promising approach for shallow-depth musculoskeletal characterization, with current strengths lying in compositional sensing and disease-related stratification. Micro-SORS, a variant of SORS with micron-scale spatial resolution, has further advanced bone diagnostics. Jansen's research group[31,33] demonstrated its utility in assessing bone microstructure (see Fig. 2B) and collagen integrity under thermal and pressure-induced stress. Their study revealed that SORS was more sensitive than conventional micro-Raman spectroscopy in detecting changes in the amide I band, which is indicative of collagen denaturation and fracture susceptibility.[38] Notingher's group has developed an efficient SORS configuration for profiling molecular composition in bone, enabling the detection of phosphate, collagen, and carbonate markers at millimetre depths.[39] These spectral markers serve as proxies for bone health and disease progression, including osteoporosis and metabolic bone disorders. Stanek *et al.*[32] as shown in Fig. 2C demonstrate the first handheld SORS-based *in vivo* assessment of adipose tissue through intact skin, extending SORS beyond hard tissues to soft metabolic targets. Using murine models of cardiometabolic disease, they show that depth-resolved SORS can detect pathology- and diet-dependent changes in lipid composition, despite overlying skin. The study highlights SORS's potential for non-invasive metabolic tissue phenotyping, while noting practical challenges for calibration and clinical translation.

Drug release

A second important direction is the use of SORS and related offset Raman methods for monitoring subcutaneous drug delivery systems and implant behaviour. Recent work has

shown that SORS can non-invasively characterize the *in situ* formation of skin implants and follow drug release kinetics in real time, demonstrating that buried pharmaceutical depots can be interrogated dynamically through overlying tissue.[40] Complementary studies using spatial offset low-frequency Raman spectroscopy[41] further show that subcutaneous drug delivery systems can be imaged *in situ*; while also capturing formulation-sensitive spectral information associated with structural or phase-related changes. These advances broaden deep Raman beyond diagnostic detection alone, showing its utility for pharmaceutical monitoring, longitudinal tracking, and characterization of buried therapeutic systems.

Cancer margin analysis

Accurate delineation of tumour margins remains a critical challenge in oncological surgery. Conventional methods, such as visual inspection and frozen section histopathology, offer limited sensitivity and specificity. A leading contributor to the clinical translation of Raman technologies is the research group led by Mahadevan-Jansen,[31,33,42] whose work has focused on developing clinic-compatible SORS instrumentation. Their modified probe design, featuring single-laser excitation and multi-offset signal collection in linear and concentric geometries, has facilitated investigations into breast cancer margin delineation and bone health assessment (see Fig. 2D). The research group led by Stone, have reported a high wavenumber probe that reads Raman signals associated with water and exploits biochemical tissue contrast to reliably distinguish tumour from non-tumour regions for intraoperative margin analysis.[43] This was explored to potentially aid reduction in re-excision rates after positive margins in breast-conserving surgery. Alternatives, such as optical coherence tomography (OCT),[15] while able to provide high resolution images, is constrained by poor contrast in most biological tissues and a shallow penetration depth. SORS, by contrast, enables molecular specific interrogation of deeper tissue layers, but with limited spatial resolution. Some recent studies have explored the integration of SORS with OCT and multispectral imaging for achieving improved diagnostic accuracy and spatial resolution.[44,45]

Cancer diagnosis and microcalcification detection

In breast cancer diagnostics, the detection of microcalcifications—typically those composed of hydroxyapatite—serves as a key biomarker for proliferative lesions and malignancy. The phosphate Raman band near 960 cm^{-1} is indicative of hydroxyapatite has been detected in phantoms at depths of up to 4 cm using SORS, when using clinically relevant calcification concentrations.[23] Stone's research group have advanced this application through transmission Raman spectroscopy (TRS), enabling rapid acquisition of high-quality spectra from excised breast tissue specimens.[46] Their clinical trials demonstrated that spectra could be obtained within 3 seconds from samples ranging from 1 to 4 cm in thickness, even in the presence of patent blue V dye used for sentinel node localisation.[23] Recent developments have also explored the use of SORS for skin-related diagnostics. For instance, SORS has been applied to assess psoriatic lesions,[47] offering a non-invasive alternative to biopsy and histopathology. These findings underscore the potential of SORS in dermatological and oncological contexts.

SORS probe development: for medicinal quality analysis and endoscopic-type applications

The development of spatially offset Raman spectroscopy (SORS) probes has evolved from benchtop optical configurations to compact, clinically and industrially deployable systems. Early SORS systems, used by us and others, were designed to separate illumination and collection regions laterally (Matousek *et al.*;[6] Yu *et al.*[48]). More recently,[49] an exploration was made using a systematic process for probe optimization: a benchtop setup tested multiple source/detector (SD) angular combinations (10°/0°, 30°/0°, 45°/0°, 45°/45°) and offset distances up to 14 mm to determine configurations balancing subsurface sensitivity and photon loss. The final fibre-optic probe, containing 19 collection fibres at offsets of 0–5 mm, was fabricated and validated for in-line pharmaceutical drying monitoring, demonstrating improved solvent detection depth compared with conventional Raman. Similarly, Yu *et al.*[48] investigated offset-dependent SORS performance across materials with distinct optical properties—Si (absorbing), PMMA (transparent), and PTFE (scattering)—revealing that scattering materials enhance subsurface recovery and validating the use of round-to-linear fibre bundles for tuneable offsets.

Across these studies, SORS probe design has progressively addressed the trade-off between depth sensitivity and signal attenuation. Larger offsets increase subsurface contribution but cause rapid loss in Raman intensity and reduced signal-to-noise ratio. Optical miniaturization and modification of Raman probes[13,49–52]—has improved portability but introduces alignment and crosstalk challenges. While Yu *et al.*[48] quantified the impact of scattering and absorption on SORS performance, real-tissue validation remains limited to controlled phantoms, leaving open questions about probe depth calibration under heterogeneous biological conditions. Furthermore, fluorescence suppression, ergonomics, and sterility requirements pose barriers to clinical deployment, particularly when using visible illumination wavelengths, rather than minimally absorbing (*i.e.* highly penetrating) NIR. Future advances should couple optical design with computational reconstruction (*e.g.*, Monte Carlo modelling or machine-learning-assisted depth deconvolution) to enhance signal fidelity. Integrating multi-offset SORS arrays with chemometric pipelines—such as PLSR or deep spectral unmixing—could enable quantitative, real-time assessment of layered biological and pharmaceutical systems. Overall, the evolution from static benchtop systems to portable, endoscopic devices marks a critical step toward routine biomedical and process-analytical SORS, though standardization and *in-vivo* validation remain essential next milestones.

Challenges

The efficacy of spatially offset Raman spectroscopy (SORS) in biomedical applications is inherently dependent upon a complex interplay of instrumental design and sample-specific

optical properties. A primary consideration is the delivery of excitation light to subsurface layers, which is influenced by tissue absorption characteristics. To manage this, SORS typically employs near-infrared (NIR) excitation wavelengths (*e.g.*, 785 nm, 808 nm, or 830 nm), which coincide with the optical transparency window of biological tissues, thereby reducing photon absorption and enhancing signal recovery.[10] However, in most biological samples, scattering dominates over absorption in this spectral region. Elastic scattering in tissue arises from refractive index heterogeneities and is commonly characterized by the scattering mean free path (l_s), which describes the average distance between scattering events, and the transport mean free path ($l_t = l_s/(1 - g)$),[53] which accounts for scattering directionality through the anisotropy factor (g). The probability and angular distribution of scattering depend on refractive index contrast, scatterer size relative to the wavelength, and the wavelength itself. For very small scatterers, scattering is nearly isotropic and strongly wavelength dependent ($\propto \lambda^{-4}$, Rayleigh scattering), whereas for larger structures such as cells, scattering is predominantly forward directed. Together, l_s and l_t determine the extent and effective randomization of photon migration in tissue; for example, in brain grey matter, l_s is approximately 50–100 μm at 630 nm and increases to around 200 μm at 800 nm. Additionally, fluorescence interference presents a significant challenge, particularly in pigmented tissues such as the liver or melanin-rich skin, and in the presence of surface features like dark or white hair. These artefacts can be mitigated through sample preparation (*e.g.*, shaving) and by employing spatial offsets that suppress surface fluorescence while enhancing subsurface Raman signals. Time-gated detection techniques[10] or shifted excitation Raman[54] also offer a viable alternative for fluorescence suppression. Collectively, these factors underscore the importance of optimising both the optical configuration and experimental protocols to maximise the depth-resolving capabilities and diagnostic reliability of SORS in clinical settings.

3. SESORS—a synergistic addition to SORS for furthering the biomedical detection potential

SESORS techniques

Surface-enhanced spatially offset Raman spectroscopy (SESORS)[7] has emerged as a powerful technique that bridges the limitations of confocal Raman, SERS, and SORS by enabling depth-resolved molecular detection with enhanced sensitivity. While confocal Raman spectroscopy is constrained by shallow penetration and dominant surface signals, SESORS significantly improves subsurface detection by combining the spatial offset geometry of SORS with the plasmonic amplification of SERS. Over time, SESORS has been refined through the optimisation of nanoparticle design, Raman tags, and excitation wavelengths, expanding its applicability across biomedical and environmental domains. Several SESORS modalities have been developed to address specific diagnostic challenges. Backscattered SESORS, with co-located excitation and collection optics, is suitable for opaque samples and includes both direct and inverse configurations, the latter allowing higher surface laser power *via* ring illumination. Transmission SESORS, which collects signals from the opposite side of the sample, is particularly effective for thick tissue analysis. Resonance SESORS further enhances sensitivity by employing Raman tags and nanoparticles tuned to the excitation wavelength. These modalities, often collectively referred to as deep Raman spectroscopy (DRS) or surface-enhanced deep Raman spectroscopy (SEDRS), each present distinct strengths and limitations. Comparative studies have shown that transmission SESORS offers better subsurface discrimination but is influenced by sample orientation and target positioning, while backscattered SESORS suffers from rapid signal attenuation with depth. Consequently, the choice of modality should be guided by the specific biomedical application and sample characteristics. A hybrid approach that integrates multiple SESORS configurations may offer synergistic benefits, enhance diagnostic accuracy and expand the scope of deep Raman spectroscopy in clinical settings.

SESORS has been shown in early research to access depths of up to 5 cm in biological tissues, thus providing exceptional depth sensitivity and selectivity.[7,8] Although in this case the non-invasiveness refers to the probing step as the application of the method requires invasive introduction of SERS-active nanoparticles (NPs), often gold, into the tissue to the target depth. The NPs are typically labelled with a Raman reporter molecule to enable their Raman sensing.[18,55–63] The NPs can be administered into tissue directly by injection into the target location.[64] SESORS can also be deployed by implanting a SERS substrate subcutaneously to enable, for example, continuous monitoring of some biologically important parameter, e_g glucose levels.[65] The SERS NPs can also be introduced intravenously to accumulate specifically in a cancer lesion aided by appropriate targeting ligands[66–69] such as antibodies or peptides. Such NPs are often also encapsulated either with polyethylene glycol[70] or silica shell.[7] Gold nanostructures that can be explored for SERS-active diagnosis and photothermal therapy have also been researched by various groups.[63,71–74] Additional useful SORS and SESORS capabilities demonstrated in recent years include an ability to monitoring temperature (T),[17,75] pH,[76] change in SERS activity due to external trigger.[77]

SERS nanostructures for SESORS

The development of SERS nanostructures has been pivotal in advancing surface-enhanced spatially offset Raman spectroscopy (SESORS) toward deep-tissue biomedical applications. Spherical gold nanoparticles (AuNPs), typically 60–100 nm in diameter, remain the most widely used due to their facile synthesis, optical stability, and well-characterized surface chemistry. Early commercial examples such as Oxonica/Cabot Nanoplex Biotags were silica-coated, SERS-labelled AuNPs.[7] The key merit of these nanospheres lies in their chemical robustness and consistent surface functionalization, yet their electromagnetic enhancement is relatively modest, limiting their sensitivity for low-abundance biomarkers at larger depths.

To address this, alternative plasmonic morphologies such as silver films over nanospheres (AgFONs) and gold nanostars have been explored. AgFONs,[78,79] used as implantable substrates for continuous glucose monitoring, provide exceptional field confinement but are non-injectable and invasive, while nanostars—owing to their branched geometry and tuneable resonances near 600–700 nm—offer superior NIR enhancement and colloidal stability, making them more suitable for *in vivo* imaging applications.

Beyond single nanostructures, nano-assemblies composed of polymer-linked gold nanoparticle clusters represent a promising strategy for enhancing signal strength at depth. Dey and co-workers, in a series of publications,[55–63] have reported different morphological designs of nano-assemblies exhibiting sub-100 nm total size, colloidal stability for injectability, biocompatibility, as well as SERS hot-spot related intensity control. One of the studies by Dey *et al.*[18] was the first to demonstrate their advantage experimentally, achieving 8 mm detection depth in animal tissue using a 785 nm laser and 2–3 mm offset SORS configuration. The interparticle coupling within these assemblies produced stronger localized electromagnetic fields and improved depth sensitivity relative to isolated nanoparticles. This structural synergy suggests that nano-assemblies can overcome the limitations of single-particle enhancement by facilitating plasmonic hot-spot networks, although their reproducibility and long-term colloidal stability remain major challenges. Additionally, their larger hydrodynamic size may impede circulation and tissue penetration, complicating clinical deployment.

Parallel to structural optimization, Raman reporter selection has emerged as a critical determinant of SESORS performance. Non-resonant tags[7,80] such as BPE and POT are chemically stable but produce relatively weak signals, whereas resonant NIR dyes[81–83] (*e.g.*, IR792, IR830, dye 823) significantly boost Raman cross-sections when paired with NIR excitation (785–830 nm). Studies by Faulds[80–84] and van Duyne[78,79,85,86] demonstrated that resonant labelling could increase signal intensity by up to 40-fold, enabling detection through tens of millimetres of porcine tissue under modest offsets. However, resonant labels can introduce photobleaching, spectral overlap, and increased cytotoxicity, requiring careful design of encapsulating shells and controlled surface chemistry. Furthermore, although Stone *et al.*[7] achieved 50 mm tissue penetration using non-resonant silica-encapsulated nanoparticles, this was under long acquisition times (300 s) and high particle concentrations, although these were 100 times less particles than that used by Keren *et al.*,[87] to measure signals at depths of 5 mm in a mouse, without deep Raman.

In summary, the progression from simple spherical AuNPs to anisotropic (nanostars) and assembled (clustered) nanostructures, coupled with resonant Raman reporters, has markedly enhanced the achievable depth and sensitivity of SESORS. The main merits of these systems include tunable plasmonic properties, strong field localization, and compatibility with NIR excitation, which collectively enable centimetre-scale Raman detection under controlled conditions. However, key challenges persist maintaining colloidal and photothermal stability under physiological environments, minimizing nanoparticle dose while preserving signal intensity, and ensuring *in vivo* safety and clearance. Clinically, the translation of these nanostructures demands the development of biodegradable, renally clearable, and resonant NIR-active probes that balance optical performance with biological compatibility. Thus, while SESORS nanostructure engineering has reached remarkable optical depths, its clinical maturity now depends on convergence between nanomaterial design, safety profiling, and regulatory compliance to realize non-invasive, real-time molecular sensing in human tissues.

4. SESORS biomedical applications

Biomarker and cellular process detection *in vivo*

Surface-enhanced spatially offset Raman spectroscopy (SESORS) has emerged as a transformative modality for *in vivo* molecular sensing, combining the subsurface sensitivity of spatially offset Raman spectroscopy (SORS) with the plasmonic amplification of surface-enhanced Raman scattering (SERS). This synergy enables non-invasive detection of molecular biomarkers, and real-time monitoring of cellular processes, at clinically relevant depths. By displacing the collection and excitation regions, SESORS enhances Raman photon collection from deeper layers while maintaining the nanometre-scale sensitivity of SERS substrates. Recent developments in nanoprobe design—such as gold nanostars, nanorods, and silica-coated plasmonic clusters—have significantly improved photostability, resonance tunability, and biocompatibility.[88–90] These advances allow multiplexed, chemically specific imaging of biomarkers under scattering biological media. However, despite progress with *in vivo* animal models, translation to human use remains limited due to tissue heterogeneity, nanoparticle clearance, and signal standardisation challenges.

Glucose and metabolic sensing

One of the earliest biomedical applications of SESORS was metabolic monitoring, particularly *in vivo* glucose detection. A proof-of-concept glucose sensing by implanting silver-film SERS substrates in rat tissue, enabling glucose quantification through overlying skin layers. Subsequent studies extended this approach to tissue phantoms and *ex vivo* models, detecting SERS-barcoded nanoparticles at depths up to 5.5 mm.[65,79] More recent work has explored carbon-nanostructured and graphene-supported SESORS biosensors to enhance sensitivity and selectivity, offering potential for miniaturised, continuous glucose monitoring devices. However, clinical adoption remains hindered by the instability of metallic nanostructures, variation in local refractive indices, and the need for long-term biocompatibility testing. Future development of encapsulated plasmonic films and NIR-II (1000–1700 nm) SESORS excitation could mitigate scattering losses and improve depth penetration for metabolic diagnostics. The hybrid technique of SESORS has demonstrated the ability to detect neurotransmitters through the skull, at physiologically relevant concentrations, offering a

promising route for non-invasive neurochemical diagnostics and early detection of neurological disorders.[91]

Cancer cell microenvironment and bioprocess analysis

The acidic and thermally heterogeneous microenvironment of cancer cells has made SESORS an attractive tool for monitoring *in situ* tumour physiology. pH-responsive SESORS (pH-SESORS) can be achieved with mercaptobenzoic acid (MBA)–functionalised gold nanoparticles, to measure intracellular or extracellular acidity, while temperature-dependent SESORS (T-SESORS) exploits the anti-Stokes/Stokes intensity ratio to estimate local nanoparticle temperatures during photothermal therapy.[75,76] Nicolson *et al.*[92] reported a landmark *in vivo* SESORS study, where resonant SERS nanostars labelled with IR792 were intravenously injected into glioblastoma-bearing mice, allowing SESORS detection through an intact skull using a 785 nm laser with a 2.5 mm spatial offset. This confirmed the feasibility of non-invasive, deep-tissue tumour imaging and margin delineation. Nonetheless, photon attenuation, fluorescence interference, and heterogeneous nanoprobe distribution still limit quantitative accuracy, underscoring the need for adaptive offset geometries and multimodal co-registration with MRI or photoacoustic imaging.

Neurotransmitter and neurochemical detection

Sharma *et al.*[85,93] demonstrated SESORS-based detection of neurotransmitters such as serotonin through approximately 3 mm of skull bone in rodent models. Using gold nanostructures excited at 785 nm with a 3 mm offset, they achieved detection at physiologically relevant concentrations ($\sim$0.1 mM). This achievement positions SESORS as a potential non-invasive neurochemical monitoring tool capable of detecting dynamic neurotransmitter fluctuations related to neurological disorders. However, practical implementation faces challenges including photon scattering through the skull, interference from autofluorescent species, and limited spatial resolution. Emerging work explores adaptive optics and deep-learning-based spectral unmixing to correct for tissue-induced distortion, offering possible paths toward clinical neurochemical diagnostics.

For *in vivo* applications, the literature shows that both SORS and SESORS are progressing toward more clinically realistic imaging and sensing scenarios. In dermatology, SORS has been explored for non-invasive monitoring of non-melanoma skin cancer, illustrating how subsurface biochemical information can be recovered from clinically accessible lesions.[94] In metabolic sensing, depth-selective micro-SORS has enabled non-invasive glucose monitoring by targeting shallow subcutaneous layers with improved specificity.[95] With SESORS, *in vivo* imaging studies have focused on improving practical performance, for example by optimizing sampling frequency to reduce acquisition time while preserving imaging quality. Other work has advanced tomographic SESORS and transmission Raman approaches for localization of nanoparticles or deep-seated SERS lesions, as well as multimodal diffuse reflectance–SORS system design for robust *in vivo* deployment.[96,97] Overall, these studies show that the field is moving beyond proof-of-principle depth demonstrations toward *in vivo* goals such as faster acquisition, improved localization, multimodal integration, and more clinically usable measurement strategies.

5. How deep do we probe with SORS and SESORS?

Collectively, the above studies demonstrate that while Raman photons can traverse centimetre-scale tissue layers, the quantitatively useful portion of the signal—capable of reliable analyte discrimination—remains limited by photon scattering, tissue absorption, and nanoparticle distribution. In this sub-section, photon scattering at depth is discussed further.

The achievable depth of Raman detection in biological tissue reflects an intricate interplay between photon transport physics, plasmonic enhancement efficiency, and biological feasibility. Mosca *et al.*[21] provided a foundational quantitative framework by introducing and discussing the 10%, 50% and 90% median signal depths—the depths up to which the given percentage of detected Raman photons originate from, as shown in Fig. 4A. Their Monte Carlo simulations and phantom experiments revealed that even with millimetre-scale spatial offsets, most photons contributing to the SORS signal arise from within 2–6 mm of the surface, with only a minor fraction emerging from deeper regions. This finding underscores that while spatial offset increases sensitivity to subsurface analytes, the effective sampling volume of SORS remains near-surface dominated. Deep-layer detection under such conditions is typically feasible only when the buried analyte exhibits strong Raman cross-sections or when its concentration is sufficiently high to dominate the weaker deep-originating photon population. That said it is important to recognise that strong signals, particularly those distinct from tissue matrix signals, generated at depth can be readily detected, below that expected if you just consider the median signals alone.

Dey *et al.* demonstrated a superior SERS nanoparticle-to-tissue signal ratio ($\sim$1 : 1), compared to conventional point Raman ($\sim$1 : 2) as illustrated in Fig. 4B, validating the practical enhancement obtained through spatial offset and plasmonic amplification. In contrast, Zhang *et al.* pushed the optical limit by achieving up to 14 cm of tissue penetration using gap-enhanced resonance Raman tags (GERRTs) in a transmission Raman setup under clinically permissible laser power ($<$0.264 W cm^{-2}). Their analytic model linked photon diffusion theory with nanoparticle brightness and beam geometry, showing that nanoprobe intensity, not simply offset distance, governs achievable depth under safe irradiance levels.

The translation of these deep Raman achievements to the clinic faces critical nanoparticle dose and safety constraints. In Dey *et al.*'s study, relatively high concentrations of PEGylated gold nanoparticles (tens of nanograms of Au per tissue gram) were used to ensure detectable signals, which, although acceptable for proof-of-principle experiments, exceed the permissible systemic doses for human applications due to concerns over long-term biodistribution, reticuloendothelial uptake, and

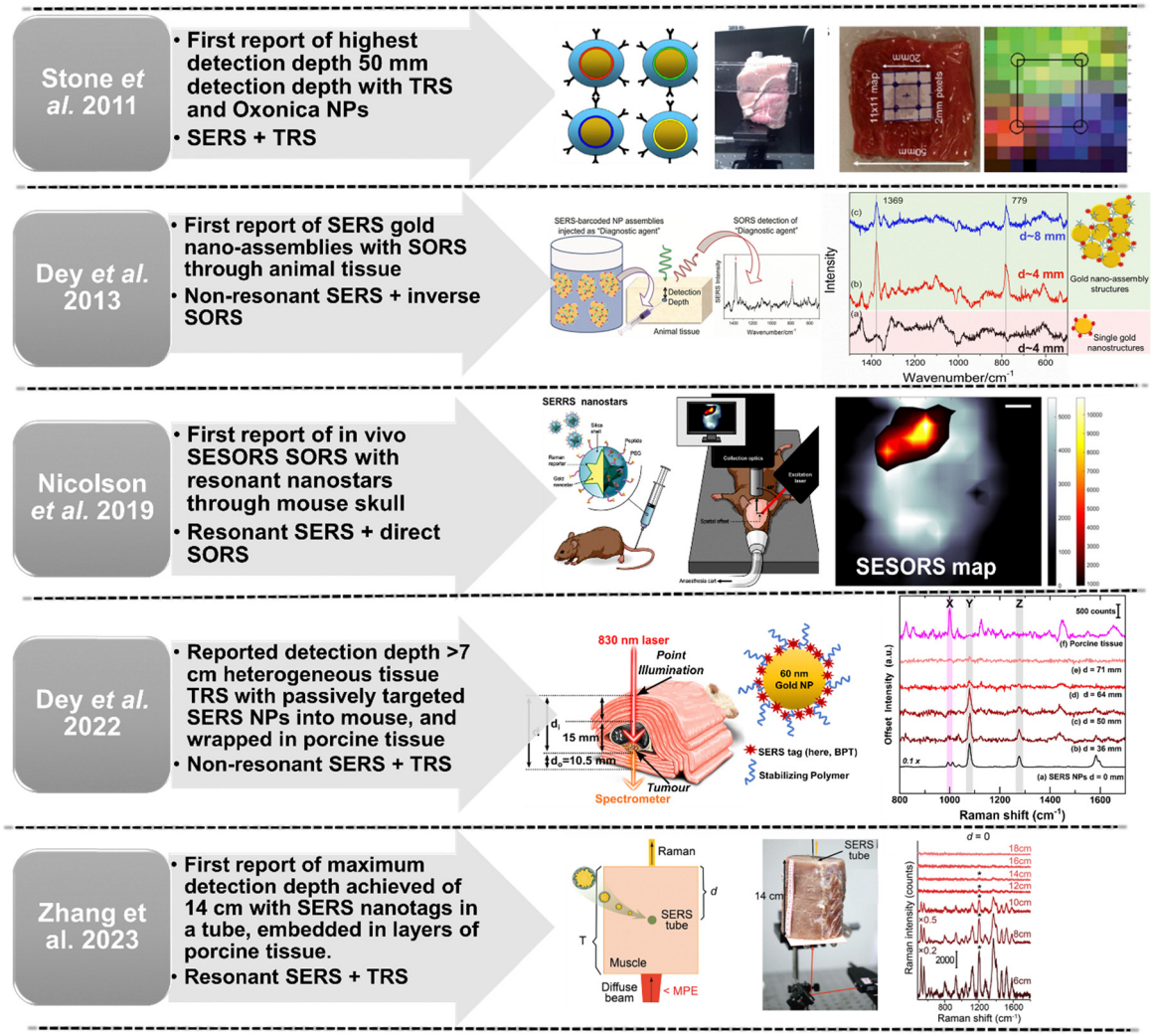

Fig. 3 SESORS discovery and applications- few key groundbreaking reports in the domain.[7,11,12,18,92] Fig. 3 [1st panel], adapted with permission from [Royal Society of Chemistry],[7] copyright 2011. Fig. 3 [2nd panel], adapted with permission from [John Wiley & Sons, Ltd],[18] copyright CC-BY 4.0 2013. Fig. 3 [3rd panel], adapted with permission from [Ivyspring International Publisher],[92] copyright CC-BY 4.0 2029. Fig. 3 [4th panel], adapted with permission from [Ivyspring International Publisher],[11] copyright CC-BY 4.0 2022. Fig. 3 [5th panel], adapted with permission from [Wiley-VCH GmbH],[12] copyright CC-BY 4.0 2022.

clearance through the liver and spleen. Similarly, the GERRTs used by Zhang *et al.*[12]—though optically superior—comprise multilayered Au–Ag–dye core–shell structures with uncertain biodegradability and potential cytotoxicity. Clinically realistic SERS assays must therefore achieve comparable brightness, at orders of magnitude lower nanoparticle concentrations (typically $<10^{-9}$ M), while maintaining optical stability and minimal toxicity. Moreover, tissue accumulation and aggregation of metallic nanoparticles can induce local optical artefacts and nonlinear field enhancement effects that distort quantitative depth measurements.

From a clinical perspective, non-invasive Raman diagnostics for applications such as breast tumour margin delineation, glioma detection through cranial bone, or metabolic monitoring in subcutaneous tissues would require reliable quantitative detection at depths of 10–40 mm with minimal nanoprobe dosage and acceptable signal-to-noise ratios. Current evidence indicates that while centimetre-scale optical reach (up to 14 cm) is achievable under optimized laboratory conditions, clinically actionable SESORS remains challenging where both laser exposure, Raman signal fidelity and nanoparticle dose and biocompatibility are serious concerns. Bridging this gap will require next-generation SERS nanoprobes with ultra-high quantum yields, especially those making use of labels in the silent region such as alkynes or those using the second optical window, near-infrared II (NIR-II, 1000–1700 nm) plasmonic resonance to reduce tissue scattering losses, and bioresorbable or renal-clearable architectures to comply with dosing limitations.[98–104]

In summary, deep Raman spectroscopy has progressed from millimetre-scale SORS probing, as constrained by photon transport theory, to multi-centimetre-scale experiments under enhanced optical conditions. Yet, for true clinical viability, advances in optical design must be matched by progress in

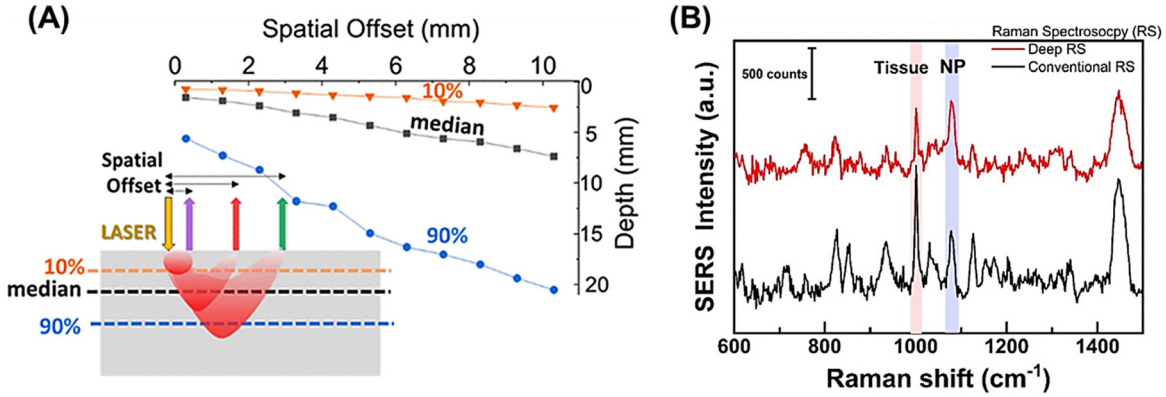

Fig. 4 What—composition and depth—does deep Raman detect? (A) How deep is the detection,[21] and (B) How much of the sub-surface vs surface composition do we visualize in deep Raman *vs.* conventional Raman.[11] Fig. 4A, reproduced with permission from [American Chemical Society],[21] copyright under CC-BY 4.0 2021. Fig. 4B, reproduced with permission from [Ivyspring International Publisher],[11] copyright CC-BY 4.0 2022.

nanoparticle pharmacokinetics, safety, and signal normalization. The next stage of development will depend on harmonizing optical depth performance with biological realism and regulatory constraints, ensuring that deep Raman sensing becomes not only physically impressive but also clinically sustainable.

6. Major breakthroughs in SESORS biomedical applications in the last 5–6 years

The ultimate utility of SESORS depends on achievable detection depth and signal fidelity under scattering conditions. While *in vivo* detection typically achieves millimetre-scale depths, surface-enhanced deep Raman spectroscopy (SEDRS) and transmission SESORS geometries have demonstrated potential for centimetre-scale sensing. Early phantom experiments by Stone *et al.* showed detection of SERS signals from 50 mm through porcine tissue using transmission setups, while Berry *et al.*[82] achieved 48 mm backscattered detection from aggregated gold nanospheres.

Across the below three reports in the last 5–6 years, SESORS (and closely related resonance SESORS, SESORRS/''surface-enhanced deep Raman''/surface-enhanced transmission Raman variants) advances along a clear translational trajectory: (i) first convincing *in vivo* disease imaging, (ii) clinically relevant depth scaling in heterogeneous tissue, and (iii) photosafe operation under exposure limits. Firstly, Nicolson *et al.*, 2019[92] established a major milestone by demonstrating the first *in vivo* SESORRS imaging of deep-seated tumours—glioblastoma in mice—through the intact skull, using integrin-targeted SERRS nanostars and showing tumour delineation consistent with MRI and histopathology. The work is impactful because it shows SESORS can overcome superficial Raman's depth/fluorescence limitations at low power density, producing high-contrast localisation where conventional (non-SORS) Raman fails. Critically, however, the demonstration is still in a small-animal regime (short pathlengths, controlled geometry), and translation hinges on issues of NP dose/clearance/toxicity of SERRS agents, robustness to inter-subject skull/tissue variability, and acquisition speed and quantification in moving, clinically realistic settings. Secondly, Dey *et al.*, 2022[11] pushed the field's depth ambition by explicitly targeting human-relevant pathlengths, reporting surface-enhanced deep Raman detection through ~71 mm of heterogeneous tissue.[4] They achieved close to real life mimic diagnosis of injected SERS NPs at a tumour site buried within centimetres of heterogeneous animal tissue, bones and blood. A key advance is methodological: instead of only showing detectability, they develop depth–signal relationships (*e.g.*, using area under the curve AUC metrics and calibration behaviour) and discuss the practical reality of injectable SERS agent detection embedded in tissues in a blind set-up, to mimic human translation. They also discuss the relevance of unavailability of required animal models to demonstrate the capabilities of human-relevant SESORS. A key limitation is that attaining such penetration depths incurs significant system- and agent-level trade-offs, including strong sensitivity to measurement geometry, tissue heterogeneity, and the requirement for adequate nanoparticle accumulation and contrast at depth. Consequently, while the study advances SESORS in terms of maximum achievable depth, it also underscores that depth alone is an insufficient clinical metric, with specificity in realistic backgrounds, reproducibility, and safety considerations becoming the dominant performance criteria. Finally, Zhang *et al.*, 2023[12] reframed the depth problem around clinical photosafety, demonstrating surface-enhanced transmission Raman measurements at laser power density below maximum permissible exposure (MPE) (reported as 0.264 W cm^{-2}), with detection through up to 14 cm *ex vivo* porcine tissue and *in vivo* imaging of nanotag-labelled ''phantom'' lesions in a mouse (1.5 cm thick, unshaved). This is a substantial translational step because it confronts a common barrier for deep Raman/SORS approaches: you can't ''solve'' depth by simply increasing power. The critique is that the most dramatic demonstrations rely on *ex vivo* slabs and phantom lesions, and transmission geometries can be harder to deploy anatomically than backscatter SORS depending on the clinical site; moreover, the approach still inherits the broader SESORS

dependency on exogenous nanotags and their delivery/targeting.

Overall, the studies collectively advance SESORS from proof-of-principle *in vivo* localisation (2019) to depth scaling in heterogeneous tissue approaching clinical relevance (2022), and then to depth demonstrations constrained by real-world exposure limits (2023). The remaining bottlenecks are less about ''can we detect a tag at depth?'' and more about agent safety and standardisation, clinically usable geometries, fast/imaging-grade acquisition, and robust specificity/quantification across heterogeneous patients and workflows.

Tissue models for deep Raman demonstration

Deep Raman/SORS development has relied on a complementary progression from phantom models to small-animal models. Phantoms are needed because they provide reproducible, ethical, and tuneable testbeds for feasibility studies, calibration, probe optimization, and benchmarking of depth sensitivity before *in vivo* deployment. In Raman specifically, this need is even stronger than in other optical methods because useful phantoms must reproduce not only scattering and absorption, but also tissue geometry and, ideally, chemical composition, since Raman contrast depends directly on molecular fingerprints. This requirement has driven the evolution from simple liquid and hydrogel phantoms toward multilayer, anatomically realistic, and more chemically representative designs, including CT-derived limb phantoms and newer skin-mimetic agarose systems with vascular channels, diffusion behaviour, and mechanical realism.[105–107] These developments have made phantoms highly valuable for optimizing offset geometry, probe placement, signal recovery, and nanoparticle-assisted deep Raman strategies under controlled conditions. However, their main limitation is that they still simplify biological reality: they cannot fully capture tissue heterogeneity, vascularization, motion, biodistribution, or dynamic physiology, and some phantom materials or additives can themselves introduce unwanted Raman or fluorescence backgrounds. As a result, small-animal models remain essential for testing *in vivo* feasibility, targeting, biocompatibility, biodistribution, and translational workflow under realistic physiological conditions. At the same time, the literature also shows their limitation for deep Raman translation: most animal models are too small to challenge the penetration depths relevant to humans, which is why many demonstrations still rely on phantoms, *ex vivo* tissues, or hybrid models that extend animal thickness artificially. Overall, phantoms are best suited to physics- and instrumentation-led optimization, whereas small-animal models provide biological validation and translational credibility; the strongest deep Raman studies therefore combine both, using advanced phantoms for controlled development and animal models for *in vivo* proof of concept.

There is a lack of an optimized animal model to demonstrate deep Raman effectiveness. To address the limitations of small animal anatomy, where mouse models are often only around 1.5 cm thick, and the cancer tumours are often visible on the skin surface, making it unrealistic to use SESORS or SEDRS. Dey and co-workers[11] designed a hybrid model combining *in vivo* tumour-bearing mice with *ex vivo* porcine tissue overlays. SERS gold nanospheres were injected subcutaneously near the tumour site, and the mouse was wrapped with porcine slices to simulate human tissue thicknesses and had achieved a detection depth of $\sim$7 cm. Large-animal and human pilot studies will be essential for validating SESORS as a reliable clinical tool for metabolic, oncological, and neurochemical diagnostics. While small-animal models are useful for assessing targeting, sensitivity, biodistribution, and pharmacokinetics *in vivo*, their anatomy does not adequately reflect the penetration depths relevant to many clinical deep-tissue applications. Importantly, penetration depth alone is not the defining metric for deep Raman imaging. As in PET and fluorescence imaging, performance also depends on specificity, sensitivity, selectivity, and biological compatibility. In this context, deep Raman and SESORS can be improved through both geometry-driven strategies, such as spatial offset collection, transmission Raman, and optimized fibre design, and brightness-driven strategies, such as SERS/SESORS nanotags and targeted contrast-agent engineering. Likewise, label-free approaches provide intrinsic biochemical information but are often sensitivity-limited, whereas agent-based methods offer stronger signal and molecular targeting but depend on delivery, biodistribution, and safety. From this perspective, hybrid models such as the mouse–porcine tissue platform developed by Dey and co-workers[11] are valuable not simply for extending achievable imaging depth, but for offering a more clinically relevant preclinical framework in which tissue geometry, instrumentation, and contrast-agent performance can be evaluated together.

7. Challenges in deep Raman translation

While deep Raman and its derivatives have achieved remarkable technical milestones, several translational barriers remain.

Firstly, the signal-to-noise trade-off at larger offsets, which are typically required to probe greater depths, together with tissue autofluorescence and the lack of standardized calibration protocols, remain major barriers to the global comparison and standardization of reported results. Equally important for clinical translation is defining the depth requirement for each application, since the key question in deep Raman is not simply how deep signals can be detected, but how deep is actually needed in a clinically meaningful setting.

Although increasing penetration depth has been a major focus of the SORS/SESORS field, with experimental demonstrations extending to up to 14 cm in tissue-like settings, depth alone is not the most informative benchmark for clinical translation. In many applications, the relevant requirement depends on the clinical geometry and endpoint. For breast margin assessment, the target is typically only 1–2 mm beneath the excised surface in cancer margin assessments with *ex vivo* detection. For bone, Raman has shown credible transcutaneous access at a few-millimetre depths at superficial sites, with

detectability established *in vivo* and quantification emerging mainly in cadaveric finger/hand models. For brain, the most realistic current human use case is surface-contact intraoperative probing, with around 500 μm penetration, whereas deeper or transcranial Raman remains largely preclinical. By contrast, metabolic sensing represents the clearest example of Raman quantifiability, because the target lies at a shallow, optically accessible depth in skin interstitial fluid.

Taken together, these studies suggest that future deep-Raman work should avoid using penetration depth alone as the primary benchmark. A more comprehensive translational framework would be to report (i) the clinically required depth range, (ii) whether the evidence comes from phantom, *ex vivo*, cadaveric, animal, or true human *in vivo* settings, and (iii) whether the endpoint is detectability or quantification. More broadly, clinical usability will depend not only on how deep signals can be recovered, but also on specificity, robustness, acquisition speed, reproducibility, and compatibility with realistic clinical workflows.

Secondly, nanoprobe safety and clearance profiles are critical for clinical adoption, necessitating long-term biocompatibility and biodistribution studies. *In vivo* SERS/SERRS/SESORS performance depends not only on optical depth, but also critically on nanoparticle delivery, biodistribution, and pharmacokinetics. Intravenous administration is often limited by rapid reticuloendothelial clearance and off-target organ uptake, intratumoral injection can improve local signal but requires prior lesion localization and procedural access, and topical or spray delivery avoids systemic clearance but remains constrained by limited tissue penetration, diffusion, and clinical practicality. In addition, injectable dose, targeting efficiency, sufficient concentration at the disease site for reliable SORS measurements, excretion pathways, and the risk of long-term accumulation in humans are all important considerations for clinical translation.

Thirdly, instrumentation improvements—such as multi-offset fibre arrays, time-gated detection, and NIR excitation—are likely to extend depth sensitivity while suppressing background interference. Instrumentation requirements for deep Raman, SORS, and SESORS vary substantially with clinical use setting, and no single architecture is optimal across all applications. Unlike conventional surface Raman, these approaches must recover subsurface photons effectively, which places additional demands on illumination–collection geometry, optical throughput, probe positioning, ambient-light control, and laser safety. For intraoperative applications,[33,43,108,109] systems must be compact, ergonomically deployable, and compatible with sterile clinical practice, while also providing rapid acquisition and near-real-time feedback. In this context, the priority is reliable subsurface interrogation within a constrained surgical workflow rather than maximum penetration depth. For bedside or outpatient use, such as transcutaneous bone, skin, or metabolic sensing, the emphasis shifts toward robustness, ease of operation, automated calibration, and reproducibility across users and sessions.[31,36,110] Here, clinically useful design depends on stable positioning, fast interpretation, and repeatable signal recovery in accessible anatomical regions. For endoscopic or minimally invasive deployment, probe architecture becomes the dominant constraint. Probe diameter, flexibility, fibre geometry, background suppression, and collection efficiency must all be balanced against anatomical access and signal quality, since miniaturization often reduces throughput and complicates background rejection.[50,111] Recent tomographic and *in vivo* SESORS studies[92,112,113] show that clinically relevant performance depends not only on depth or contrast-agent brightness, but also on acquisition speed, spatial sampling strategy, and stable measurement geometry in heterogeneous tissue. Overall, a translationally strong deep Raman/SORS/SESORS instrument is one that delivers safe, reproducible, and clinically actionable subsurface measurements within the constraints of the intended clinical environment, rather than one that simply maximizes penetration depth under idealized conditions.

Future research should also integrate SESORS data with complementary imaging modalities and machine learning-based spectral analysis to enhance diagnostic specificity.

8. Potential for deep Raman in translational diagnostics

Despite two decades of development in spatially offset Raman spectroscopy (SORS) and a decade of progress in its surface-enhanced variants—SESORS and SEDRS—their translation into biomedical applications remains both promising and complex. From an application standpoint, the integration of SORS with advanced multivariate analysis has increased both probing depth and biochemical specificity, enabling discrimination of subsurface tissue variations—such as tumour margins or metastatic lymph nodes—that are beyond the reach of conventional Raman systems. Confocal and endoscopic Raman probes have been developed to access these otherwise inaccessible regions.[114] Looking ahead, further progress in SORS is likely to depend on improved system calibration, more effective suppression of fluorescence and matrix contributions, and tighter integration with complementary imaging modalities to enhance robustness, reproducibility, and diagnostic accuracy in *in vivo* applications.

The evolution of optical engineering, including advances in laser sources, spectrometer miniaturisation, and fibre-optic probe design, has facilitated the emergence of clinic-compatible deep Raman systems. While commercial systems such as the Agilent handheld offset Raman device have found widespread use in industrial quality control, their biomedical utility so far remains limited.

There have been multiple studies registered in the UK for Clinical trials (ISRCTN, The UK's Clinical Study Registry) 13 completed and 4 ongoing—of conditions like eye diseases, cancer, musculoskeletal diseases, surgery *etc* employing Raman in some scope. A search of SORS-related clinical trials indicates that the current clinical landscape for Raman-based human studies remains relatively limited and is dominated by Raman fibre-probe, endoscopic, or transcutaneous approaches, rather

than explicitly SESORS-labelled or deep-Raman trial programs. The clearest registry example of human SORS is NCT02814591, which applies spatially offset Raman spectroscopy to the non-invasive assessment of human bone quality. Other registered studies show broader clinical interest in *in vivo* Raman probe deployment, including transcutaneous Raman analysis of deep wound soft tissue and underlying bone (NCT02202668), intravesical Raman measurements in bladder tissue (NCT05124106), Raman-based assessment of hepatic steatosis (NCT02621853), and *in vivo* bile-duct Raman spectroscopy for extrahepatic cholangiocarcinoma (NCT06964425). Collectively, these studies suggest that clinical translation has progressed most clearly through accessible fibre-based or transcutaneous implementations, while explicit SESORS and more advanced deep Raman strategies appear, at least from current ClinicalTrials.gov records, to remain largely preclinical or not distinctly categorized under those terms in human trial registration.

The clinical adoption of SESORS is hindered by the need for exogenous SERS agents, which, although beneficial for detecting non-inherent disease markers, raise questions regarding biocompatibility, systemic clearance, and regulatory approval. Notably, SESORS has achieved detection depths exceeding 14 cm in heterogeneous tissue, a milestone that parallels the anatomical thickness of major human muscle groups. These achievements have been enabled by tailored nanostructures, optimised SERS labels, and innovative Raman geometries. However, critical questions persist regarding the necessity of probing beyond these depths in clinical contexts and the feasibility of *in vivo* compatibility for SESORS systems. Addressing these challenges requires concerted efforts across several domains: the development of advanced, user-friendly instrumentation; standardisation of protocols for reproducibility and regulatory compliance; engineering of biocompatible and application-specific nanoparticles; and the creation of intuitive data analysis platforms. Furthermore, interdisciplinary collaboration among scientists, engineers, clinicians, and industry stakeholders is essential to accelerate the clinical translation of these technologies. The recent progress in micro-SORS and SORS probes for endoscopic applications, handheld deep Raman systems, and in vivo-compatible SERS nanostructures underscores the potential of Raman spectroscopy to transition from laboratory research to clinical practice with its future success depending on resolving these multifaceted challenges through sustained innovation and modifications.

Conflicts of interest

PM and NS have several granted and pending patents in the field of SORS and its derivatives NS has granted patents on *in vivo* Raman probes. PM also provides technical consultancy to Agilent Technologies.

Data availability

No data is present in connection with this review article.

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