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AI–nano-driven surface-enhanced Raman spectroscopy for marketable technologies

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The 50th anniversary of its discovery underscores surface-enhanced Raman spectroscopy (SERS) as one of the oldest and most dynamic branches of nanoscience and nanotechnology. The time has come for nanostructure-based SERS to integrate artificial intelligence (AI) tools and overcome current commercialization challenges.

Fifty years ago, the groundbreaking research conducted by Fleischmann, Hendra, and McQuillan at the University of Southampton set the stage for the emergence of surface-enhanced Raman spectroscopy (SERS)[1]. Their paper on exceptionally high-quality surface Raman spectra immediately captured the attention of Van Duyne and Jeanmaire from Northwestern University, who meticulously replicated and scrutinized the findings. Subsequently, they unveiled a remarkable surface enhancement effect of ~10^5–10^6 times[2], challenging the established principles of Raman spectroscopy.

This discovery sparked immense interest within the scientific community, fuelling a surge of enthusiasm to unravel the unexpected enhancement and explore the analytical potential of SERS, particularly its exceptional surface sensitivity. However, this wave of excitement was tempered by the realization that the enhancement heavily relied on nanostructures (the term 'nano' was not yet in use at that time) consisting of free-electron metals with poorly characterized and hard-to-control morphologies. The limited material generality and lack of control significantly impeded the progress of SERS from the 1980s to the mid-1990s, resulting in a decline in the number of publications on SERS compared to traditional Raman spectroscopy.

The resurgence of SERS went hand-in-hand with advancements in nanotechnology in the 1990s, marking a new era for SERS. Significant milestones were achieved, such as the first experimental correlation of the SERS effect with nanoparticle size in 1995, the demonstration of single-molecule sensitivity in 1997, the invention of tip-enhanced Raman spectroscopy (TERS) in 2000 and later the demonstration of sub-nanometre and even single-bond TERS. The development of shell-isolated nanoparticle-enhanced Raman spectroscopy (SHINERS) in 2010 broadened the materials and morphology generality of SERS. The demonstration of femtosecond SERS in 2011 provided valuable insights into molecular dynamics at nanoparticle surfaces. With these advancements, SERS solidified its position as one of the cornerstones of nanoscience and nanotechnology, with 4,000 publications annually[3,4].

Despite these outstanding accomplishments in fundamental research, the transition into commercially viable techniques has been surprisingly sluggish. This trend is unexpected considering the numerous advantages SERS offers, such as high sensitivity and high spectral, spatial, and temporal resolutions. The first commercial SERS company, Nanoplex Technologies Inc., was established by Michael Natan in 2002. Despite over two decades of commercialization development, also by several other companies, the global market value of SERS remains relatively modest at US$150 million in 2023, with a projected annual growth rate of less than 8%. The divergence between the explosive growth in fundamental studies and translation in commercial products is due to the differing priorities in these two realms: commercial applications prioritize practical and complex analyte analysis over extreme sensitivity. As illustrated in Fig. 1, fundamental research often focuses on simplified, single-species or standard resonant molecules. In contrast, commercialization efforts must tackle the complex task of detecting and differentiating multiple molecular species (often in the tens) in real-world samples like food and blood, while also accounting for intricate intermolecular interactions present in these systems.

To expedite the adoption of SERS as a commercially versatile analytical tool, it is essential to make further advancements in materials stability, versatility, and measurement reliability. (Note that these developmental bottlenecks may not be specific to SERS alone but are common challenges faced by many other nanotechniques.)

Nano-driven SERS

Essentially, SERS is characterized by a tripartite interaction involving photons, molecules, and nanostructures[5]. As a result, it inherits both the advantages and drawbacks of nanotechnology. For instance, SERS leverages the substantial local electric field enhancement produced by plasmon resonance in metallic nanostructures, facilitating a single-molecule-level detection limit. However, such enhancement is limited to specific metal nanostructures, resulting in restricted material and morphological versatility[3]. Moreover, these nanostructured metals are intrinsically unstable due to the high surface energy, critically impacting the reproducibility and reliability of SERS measurements.

Stability plays a crucial role in determining the commercial success of numerous nanostructure-based products, and SERS/TERS/SHINERS active materials are not immune from this issue. Free-electron metal nanostructures can offer the highest enhancement in SERS, but at room temperature the high mobility of atoms can lead to nanoscale reconstructions on the metal surface[4]. Additionally, the mobility of analyte molecules on such surfaces makes it difficult to accurately characterize and control the surface structure of nanostructures. This structural instability is further exacerbated under laser illumination due to local heating effects, resulting in fluctuations in the SERS spectral intensity, a phenomenon known as signal 'blinking'. The removal of a single atom from a surface within the hotspot with a 1 nm gap can lead to a change in signal intensity from one to two orders of magnitude. The relationship between nano-structural stability and sensitivity in SERS can be roughly described using a sort of uncertainty principle by which "the greater the enhancement, the less it is possible to know about the atomic-level detail of the substructures involved"[6].

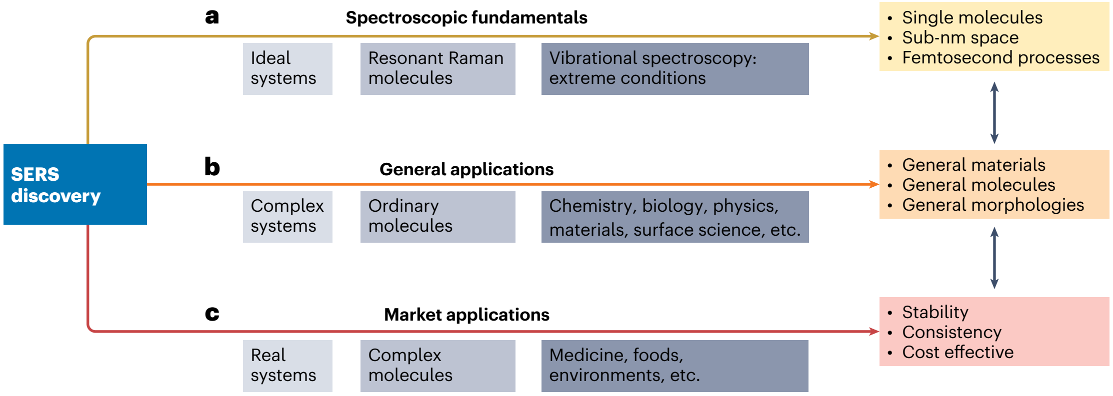

Fig. 1 | Since its discovery, SERS has developed along three different directions, each with its own focus, priority, and bottlenecks. a, Research toward spectroscopic fundamentals aims to achieve ultimate sensitivity and resolution using idealized conditions like low temperatures and resonant molecules. These conditions, however, may not be practical for all applications and are often limited to specific molecules or a few 2D materials as the substrates. **b**, General applications seek to integrate SERS across various scientific fields by exploring diverse substrates, morphologies, and molecular generality, including widely used non-resonant molecules. The main technical challenge lies in adapting SERS to a broad range of experimental setups and conditions. **c**, Commercial and market applications focus on complex analyses (such as proteins, viruses, food additives, and so on) and environments encountered in real-world applications, which prioritize to managing the intricate interplay among molecules, photons, and nanostructures within real systems. Ensuring spectral signal consistency and stability is crucial for successful market integration and widespread adoption, requiring the development of reliable, consistency, reproducible, and cost-effective solutions.

Another aspect to consider in SERS is storage stability. Commercialization often requires nanostructures to have a long shelf life of around two years, while maintaining high reproducibility. However, SERS nanoparticles are thermodynamically unstable and susceptible to aggregation, contamination, and degradation in ambient environments, which typically limits their lifespan to a few weeks. To extend storage stability, the surface of these nanostructures are usually modified with protective ligands or functional groups[5]. However, the presence of these ligands can occupy surface adsorption sites, resulting in a reduction in detection sensitivity and selectivity for analytes. Shell-isolated nanoparticles (SHINs)[7] is a promising approach to enhancing stability and applicability due to the chemically and electrically inert shells of the nanoparticles. However, this increased stability often comes at the cost of reduced sensitivity, as thicker shells result in a weaker SERS signal. To maintain sufficient detection sensitivity, the dielectric shell used in SHINs should be about 2-nm thick. At this thickness, it becomes challenging to maintain a defect-free structure and ensure stability over extended periods of several months to years. This trade-off still presents a significant challenge for industry professionals.

Currently, most SERS-detectable analytes are strong adsorbates with large Raman scattering cross-sections. It is desirable to expand the reliability of SERS detection to include weakly adsorbed molecules[5] and various material surfaces and interfaces.

Additionally, reliable and reproducible SERS signals rely on establishing standard protocols for sample pretreatment, measurement, and analysis procedures tailored to a variety of practical scenarios[4,5]. To achieve this, the academic and industrial research communities should come together and carry out intra-batch and inter-batch uniformity studies.

Marketable technology also hinges on addressing cost-related considerations. Various practical scenarios require on-site detection of analytes. For food safety, point of care testing, and environmental monitoring, traditional laboratory spectrometers are impractical. A great opportunity for the SERS community will be to integrate suitable SERS substrates with portable Raman instruments that can replace laboratory spectrometers for rapid on-site detection. Although miniaturization inevitably leads to compromised resolution and limited detection sensitivity, fabricating on-chip Raman spectrometers, with the possibility of incorporating SERS into personal user terminals, such as smartphones, remains a goal for commercialization of the SERS technique.

AI-assisted SERS

In the current nano-driven SERS research paradigm, breakthroughs rely on symbiosis between simulations and experimental approaches. However, the gap between these two methodologies still presents significant obstacles. As shown in Fig. 2a, the current workflow involves designing optimized nanostructures with numerical simulations, which set parameters based on empirical knowledge to predict SERS performance. This approach is often inefficient and costly, with unclear connections between optical responsiveness and synthesis parameters, especially when atomic-level precision control of the nanostructure is required. Consequently, development still heavily depends on experimental trial and error. Furthermore, interpreting spectrum–structure correlations in complex environments is challenging due to intricate molecule–nanostructure interactions, which typically alter SERS spectra in multiple ways, thereby affecting the reliability of SERS analysis. Given these bottlenecks, recent advancements in artificial intelligence (AI) should be leveraged. These AI advancements could address challenges in both the fundamental understanding and marketability of SERS.

We categorize AI-assisted nano-driven SERS research into three aspects: nanostructure guiding, acquisition optimization and spectrum–structure correlation (Fig. 2b). The scientific database for AI models can be established by compiling various types of data from high-precision experimental measurements (including spectroscopy, and scanning electron microscopy), high-throughput theoretical

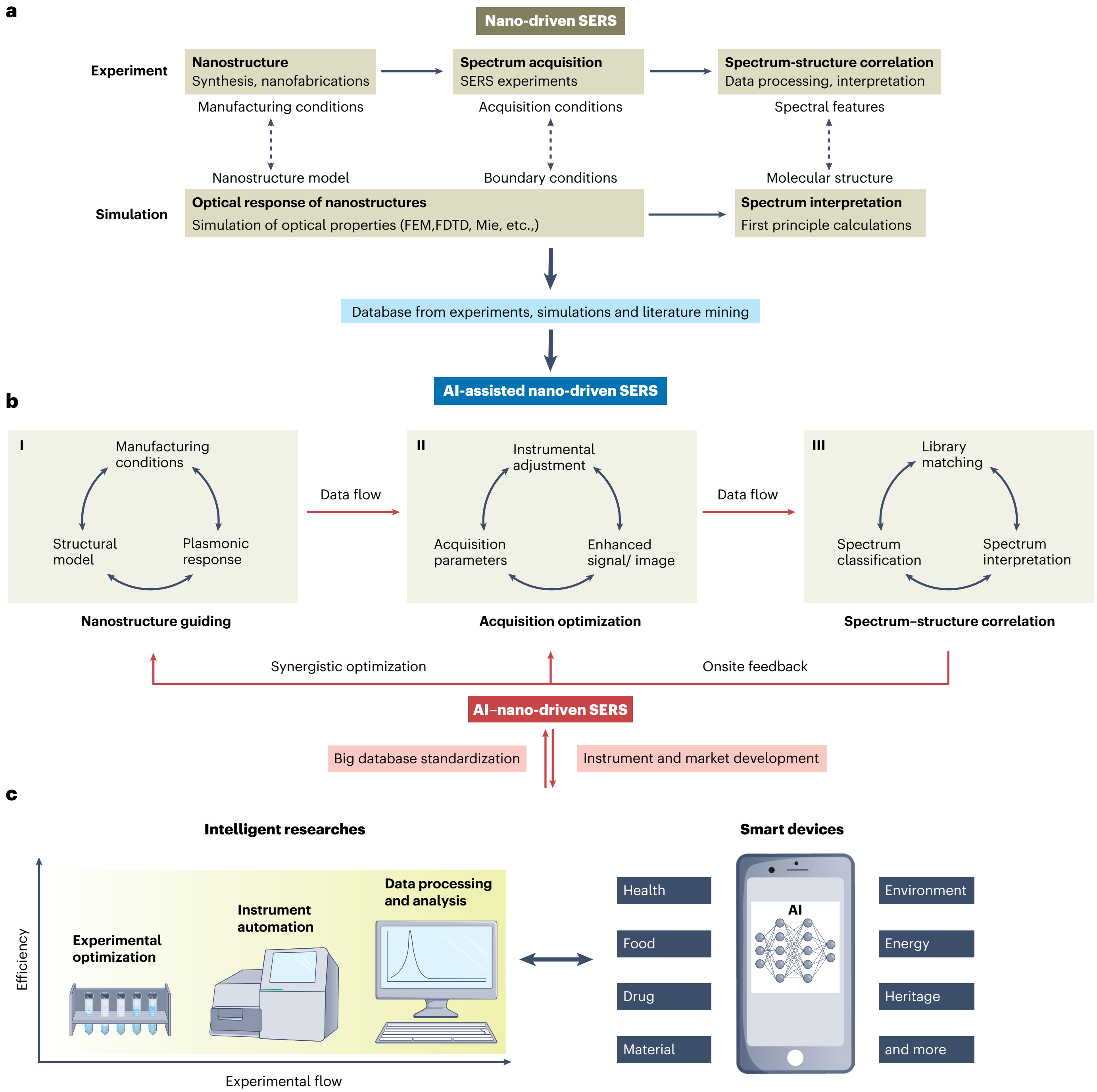

Fig. 2 | From nano-driven SERS to AI-assisted and AI–nano-driven SERS research paradigms. a, The workflow of nano-driven SERS research. Close collaboration between experiment and theory is essential throughout all stages of these procedures. Listed are typical parameters that significantly influence the outcomes of both experiments and calculations, which are generally determined by prior knowledge and experience. However, the connection between experimental parameters and theoretical ones is vague, as indicated by the dashed arrows. **b**, The workflows of AI-assisted nano-driven SERS and AI–nano-driven SERS. In AI-assisted nano-driven SERS, the trained AI model improves efficiency and accuracy either in nanostructure design and manufacture, instrument optimization, or spectral interpretation. AI–nano-driven SERS is proposed to integrate those modules together to form a self-driven closed loop. It achieves real-time on-site feedback from the final interpreted results to guide nanostructure manufacturing and instrumentation adjustments, as indicated by the red arrows. The newly generated data within the loop is essential for self-optimization. **c**, Two typical AI–nano-driven SERS-enabled market applications include intelligent research instruments for scientific research (left) and miniaturized smart devices for personal users (right).

calculations (such as optical property simulations, and DFT calculations), and extensive literature mining[8].

AI-assisted nanostructure guiding mainly consists of three correlated components: manufacturing condition, structural model and plasmonic response prediction. Pre-trained AI models can quantitatively establish complex high-dimensional correlations between these components (Fig. 2b, part i). This enables inverse design methods of the desired plasmonic response to avoid the trial-and-error approach of conventional workflows[9], reducing both the time and cost associated with SERS nanostructure preparation. Additionally, AI-assisted guiding can predict novel SERS nanostructures that would not have been otherwise explored. The consistency of SERS nanostructures can also be improved by utilizing AI-guided automated manufacturing, such as robotic AI-chemist systems[8,10].

The AI-assisted acquisition optimization process (Fig. 2b, part ii) includes instrument adjustment, acquisition parameters and enhanced signals or images. The process enables suppression of instrumental noise, and extraction of meaningful signals from low signal-to-noise-ratio data, thereby improving detection limits. For example, integrating image recognition algorithms with automated instrument control and feedback can efficiently locate nanostructures of interest, perform data acquisition, and obtain high-throughput standardized experimental data[11], thereby reducing fluctuations in SERS spectra. Through data augmentation, it is possible to restore and extract spectral features from low-quality and low-resolution spectra or images[12], relaxing restrictions on detection sensitivity or resolution. For example, fully opening the entrance slit of a Raman spectrometer traditionally increases signal throughput at the cost of energy resolution. However, integrating AI algorithms can accurately restore energy resolution, facilitating an improvement in the signal-to-noise ratio[13]. This is particularly crucial for miniaturized Raman devices. With the improved spectral sensitivity achieved by integrating AI, more inert and stable SERS nanostructures could be employed in practical applications.

AI-assisted spectrum–structure correlation (Fig. 2b, part iii) comprises library matching, spectrum classification and spectrum interpretation. A well-trained AI model can offer rapid spectral data processing, analysis, interpretation, and extraction of hidden patterns and correlations in massive datasets. As a result, an accurate prediction of molecular structures from spectra[14] can be realized based on the patterns recognized in the trained dataset. This is particularly beneficial for the rapid detection and quantification of trace species, and subsequent expert-free decision-making, in point-of-care (POC) detection scenarios.

AI–nano-driven SERS

It should be emphasized that in the current landscape of AI-assisted nano-driven SERS research, efforts have primarily concentrated on these three individual modules independently, showing some potential to address issues of stability, consistency, and sensitivity. We anticipate a synergistic approach that integrates these sub-functional modules into a seamless, self-driven, closed-loop process (red arrows in Fig. 2b) for continuous optimization, which we term AI–nano-driven SERS.

In AI–nano-driven SERS, the key distinguishing feature from previous AI-assisted approaches is the continuous data exchange and generation process within the loop (indicated by red arrows). Initially, starting from the desired spectral response, suitable SERS materials are inversely designed and then automatically synthesized by a higher-level robotic system. Both the synthesized materials and corresponding data are transmitted to the spectral acquisition module, where the instrument automatically adjusts the optical path and optimizes the measurement conditions to obtain high-quality spectra based on the transmitted synthesized data. The data analysis module rapidly establishes spectrum–structure correlations that are utilized by the central AI module for decision making, on-site feedback and synergistic optimization. The central AI module adjusts the working conditions of the analyte devices, informs the sample preparation and data acquisition modules for further adjustments, and initiates another cycle of the loop. The detection sensitivity and analysis speed of each sub-functional module determines the flow rate of the whole loop; ensuring the efficient operation of each module is a pre-condition.

Real-time AI–nano-driven SERS analysis would be particularly powerful in industrial scenarios. Taking the example of SERS monitoring of battery failure, real-time analysis of characterization data during the operational process would enable immediate adjustments based on rapid feedback, leading to optimized device performance. Contrast this with the traditional spectroscopic characterization scenario where signal acquisition and analysis are done separately, typically requiring days to fully process data and draw conclusions, which would then inform subsequent experimental cycles.

These AI-driven advancements are poised to reshape the future market potential for SERS-based products, which can be broadly divided into two main segments (Fig. 2c). The first includes research-grade products, designed for intelligent spectroscopic research in laboratory settings. The second comprises application-grade products, focusing on portable smart devices for field-based or POC use. Both segments can greatly benefit from AI–nano-driven SERS techniques in terms of enhanced consistency, stability, and applicability. The symbiotic relationship between product application and technological advancement underscores the potential for rapid progress in the field of SERS-based analytics.

The long-term and ultimate goal is to fully leverage the overwhelming advantage of AI to autonomously learn and evolve the SERS methods and techniques. As training parameters and data volume reach critical thresholds, large-scale AI models may exhibit emergent capabilities[15], potentially leading to the creation of new optical materials, structures, and working principles. This approach would be distinct from the conventional workflow (Fig. 2a) and would introduce unpredictable instrument designs and analytical power.

Our aspiration is for this Comment to ignite a spark in readers to embrace AI as an enabling technology for expanding the reach of nanostructure-based SERS, towards more commercially viable applications.

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Competing interests

The authors declare no competing interests.