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Electronic Raman Scattering Calibration for Quantitative Surface-Enhanced Raman Spectroscopy and Improved Biostatistical Analysis

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Abstract : Despite its ultrasensitive detection capability, surface-enhanced Raman spectroscopy (SERS) faces challenges as a quantitative biochemical analysis tool due to the significant dependence of local field intensity in hotspots on nanoscale geometric variations of plasmonic nanostructures. Therefore, despite enormous progress in plasmonic nanoengineering of high-performance SERS devices, it is still challenging to quantitatively correlate the measured SERS signals with the actual molecule concentrations at hotspots. A significant effort has been devoted to developing SERS calibration methods by introducing internal standards. It has been achieved by placing Raman tags at plasmonic hotspots. Raman tags undergo similar SERS enhancement at the same hotspots, and ratiometric SERS signals for analytes of interest can be generated with reduced dependence on geometrical variations. However, using Raman tags still faces challenges for real-world applications, including spatial competition between the analyte and tags in hotspots, spectral interference, laser-induced degradation/desorption due to plasmon-enhanced photochemical/photothermal effects. We show that electronic Raman scattering (ERS) signals from metallic nanostructures at hotspots can serve as the internal calibration standard to enable quantitative SERS analysis and improve biostatistical analysis. We perform SERS with Au-SiO_2 multilayered metal-insulator-metal nano laminated plasmonic nanostructures. Since the ERS signal is proportional to the volume density of electron-hole occupation in hotspots, the ERS signals exponentially increase when the wavenumber is approaching the zero value. By a long-pass filter, generally used in backscattered SERS configurations, to chop the ERS background continuum, we can observe an ERS pseudo-peak, IERS. Both ERS and SERS processes experience the $|E|^4$ local enhancements during the excitation and inelastic scattering transitions. We calibrated IMRS of 10 μM Rhodamine 6G in solution by IERS. The results show that ERS calibration generates a new analytical value, ISERS/IERS, insensitive to variations from different hotspots and thus can quantitatively reflect the molecular concentration information. Given the calibration capability of ERS signals, we performed label-free SERS analysis of living biological systems using four different breast normal and cancer cell lines cultured on nano-laminated SERS devices. 2D Raman mapping over 100 μm × 100 μm, containing several cells, was conducted. The SERS spectra were subsequently analyzed by multivariate analysis using partial least square discriminant analysis. Remarkably, after ERS calibration, MCF-10A and MCF-7 cells are further separated while the two triple-negative breast cancer cells (MDA-MB-231 and HCC-1806) are more overlapped, in good agreement with the well-known cancer categorization regarding the degree of malignancy. To assess the strength of ERS calibration, we further carried out a drug efficacy study using MDA-MB-231 and different concentrations of anti-cancer drug paclitaxel (PTX). After ERS calibration, we can more clearly segregate the control/low-dosage groups (0 and 1.5 nM), the middle-dosage group (5 nM), and the group treated with half-maximal inhibitory concentration (IC50, 15 nM). Therefore, we envision that ERS calibrated SERS can find crucial opportunities in label-free molecular profiling of complicated biological systems.

Keywords : cancer cell drug efficacy, plasmonics, surface-enhanced Raman spectroscopy (SERS), SERS calibration
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