

Contents

<i>List of contributors</i>	<i>xi</i>
1. Principles of surface-enhanced Raman spectroscopy	1
Xiang Wang, Guokun Liu, Ren Hu, Maofeng Cao, Sen Yan, Yifan Bao and Bin Ren	
1.1 Introduction	1
1.2 Surface plasmon resonance	3
1.3 Optical properties of metals	4
1.4 Local field enhancement	6
1.5 Surface-enhanced Raman spectroscopy enhancement and $ E ^4$ approximation	8
1.6 Choice of metals	10
1.7 The effect of size and shape on the field enhancement	11
1.8 Hot spots and various configurations for SERS	14
1.9 Estimation of the surface enhancement factor	18
1.10 Chemical mechanism	19
1.11 Spectral analysis	20
1.12 Selection of SERS substrates	23
1.13 SERS detection modes	24
1.14 Key to the success of SERS measurements	26
References	27
2. Nanoplasmonic materials for surface-enhanced Raman scattering	33
Shi Xuan Leong, Yong Xiang Leong, Charlynn Sher Lin Koh, Jaslyn Ru Ting Chen and Xing Yi Ling	
2.1 The role of nanoplasmonic materials in surface-enhanced Raman scattering enhancement	33
2.2 Metallic nanoplasmonic materials	36
2.2.1 Shape-controlled synthesis of individual nanoparticles (0D/1D)	36
2.2.2 Two-dimensional platforms for electromagnetic field enhancement	42
2.2.3 Three-dimensional platforms for electromagnetic field enhancement	48
2.2.4 Analyte manipulation strategies	53
2.3 Nonconventional surface-enhanced Raman scattering platforms	63
2.3.1 Bimetallic systems	63

2.3.2	Hybrid nanoplasmonic platforms	65
2.4	Conclusion and outlook	72
	References	73
3.	Experimental aspects of surface-enhanced Raman scattering for biological applications	81
	Shuping Xu	
3.1	Combination ways of surface-enhanced Raman scattering substrates with the analytical systems	81
3.1.1	Colloidal metal nanoparticles	82
3.1.2	Solid-supported metal nanostructures	92
3.1.3	Other unique surface-enhanced Raman scattering substrates	97
3.2	Laser-related issues	99
3.2.1	Laser wavelength selection according to surface plasmon resonance	99
3.2.2	Laser wavelength and surface-enhanced resonance Raman scattering	101
3.2.3	Laser power setting and defocusing for avoiding photodamage	102
3.2.4	Light penetration depth for <i>in vivo</i> detection	103
3.3	Reproducibility and reliability	105
3.3.1	Mean spectra	105
3.3.2	Homogenization of sample	105
3.3.3	Controlled immobilization and orientation	107
3.3.4	Purification of the surface of surface-enhanced Raman scattering substrates	108
3.3.5	Contributions of media and reagents	108
3.3.6	Integration of surface-enhanced Raman scattering with microfluidics	108
3.3.7	Internal standard method	109
3.3.8	Reporters having bands in silent range	110
3.4	Raman data-related issues	110
3.4.1	Data processing	110
3.4.2	Chemometric sorting algorithm	111
	References	113
4.	Label-free surface-enhanced Raman scattering for clinical applications	125
	Alois Bonifacio	
4.1	General aspects	125
4.1.1	Defining <i>label-free</i> surface-enhanced Raman scattering	125

4.2	Label-free SERS and the complexity of biological samples	127
4.3	Clinical needs and analytical strategies	128
4.4	Experimental aspects	132
4.4.1	Preanalytical sample processing	132
4.4.2	SERS substrates and the nano–bio interface	134
4.4.3	Excitation wavelengths	137
4.4.4	Common artifacts and anomalous bands	140
4.5	Study design and data analysis	141
4.5.1	Sources of variability	141
4.5.2	Data structure and sample size	146
4.5.3	Data analysis: preprocessing, representation, and modeling	149
4.6	Spectral interpretation	158
4.7	Perspectives and challenges	163
	References	165
5.	Surface-enhanced Raman scattering nanotags design and synthesis	171
	Xiao-Dong Zhou, Xue Li and Ai-Guo Shen	
5.1	SERS nanotags and its optical properties	171
5.2	Clinical application of SERS nanotags: strategies and essence	173
5.3	SERS nanotags design and synthesis	174
5.3.1	Highly bright SERS nanotags: substrate construction	175
5.3.2	Weak-background SERS nanotags: signal output	184
5.3.3	Low-blinking SERS nanotags: surface coating	198
5.3.4	Multifunctional SERS nanotags: materials combination	205
5.4	Summary and prospect	211
	References	215
6.	Surface-enhanced Raman spectroscopy for circulating biomarkers detection in clinical diagnosis	225
	Yuan Liu, Nana Lyu, Alison Rodger and Yuling Wang	
6.1	Introduction	225
6.2	Sample preparation and detection methods	228
6.3	Circulating tumor cells	229
6.3.1	Features and current techniques for circulating tumor cells analysis	229
6.3.2	SERS strategy for CTCs analysis	230
6.3.3	SERS-based assays for CTCs analysis in clinical samples	233
6.3.4	Insights on SERS-based CTCs analysis in a clinical setting	236
6.4	SERS analysis of extracellular vesicles	237

6.4.1	Biological roles and current analysis techniques of extracellular vesicles	237
6.4.2	SERS strategies for EVs detection and characterization	238
6.4.3	SERS-based assay for EV analysis with clinical samples	239
6.4.4	Insights on SERS-based EVs analysis with clinical setting	244
6.5	SERS analysis of circulating tumor-derived nucleic acids	245
6.5.1	Biological significance and current analysis techniques for ctNAs	245
6.5.2	SERS strategies for ctNAs analysis	248
6.5.3	ctDNA analysis by SERS	252
6.5.4	ctRNA analysis by SERS	257
6.5.5	Insights into SERS-based ctNAs analysis with clinical samples	261
6.6	Tumor-associated proteins	262
6.6.1	Clinical significance and current analysis techniques of circulating proteins	262
6.6.2	SERS-based strategy for protein analysis	263
6.6.3	Insights on SERS-based assays for disease-associated protein detection	270
6.7	Conclusions and perspectives	270
	References	271
7.	Surface-enhanced Raman spectroscopy-based microfluidic devices for in vitro diagnostics	281
	Anupam Das and Jaebum Choo	
7.1	Introduction	281
7.2	Various surface-enhanced Raman spectroscopy-based microfluidic devices for in vitro diagnostics	283
7.2.1	Application of paper-based microfluidics	284
7.2.2	Magnetic particle-based microfluidics	288
7.2.3	Gold-patterned microarray-embedded microfluidic platforms	292
7.2.4	Continuous-flow microfluidics	294
7.2.5	Surface-enhanced Raman spectroscopy assays using droplet-based microfluidics	295
7.3	Summary	299
	Acknowledgment	299
	References	299
8.	SERS for sensing and imaging in live cells	303
	Janina Kneipp	
8.1	Recent trends in SERS from animal cells: probe of cellular biochemistry	303
8.2	Biomolecular SERS from intracellular nanoprobe	304

8.3	Probing lipid-rich environments in pathology	307
8.4	SERS for monitoring of drug action	310
8.5	Composite SERS probes for intracellular applications with different physical functions	313
	Acknowledgments	319
	References	319
9.	iSERS microscopy: point-of-care diagnosis and tissue imaging	327
	Yuying Zhang, Vi. Tran, Mujo Adanalic and Sebastian Schlücker	
9.1	Point-of-care diagnosis	327
9.1.1	Principle of a lateral flow assay	329
9.1.2	SERS-based lateral flow assay	332
9.1.3	SERS-based multiplex lateral flow assay	337
9.1.4	Portable Raman/SERS-POC reader	343
9.2	Imaging	345
9.2.1	iSERS microscopy on cells	347
9.2.2	iSERS microscopy on tissues	356
9.3	Summary and perspectives	365
	References	366
10.	Surface-enhanced Raman spectroscopy for cancer characterization	373
	Wen Ren and Joseph Irudayaraj	
10.1	Introduction	373
10.2	SERS diagnosis of cancer biomarkers	375
10.3	SERS detection of nucleic acid sequence indicators in cancer	378
10.4	SERS diagnosis based on other indicators	380
10.5	Multifunctional SERS substrates for diagnosis and therapy	381
10.6	SERS imaging for cancer imaging and delineation	385
10.7	Summary	389
	References	389
11.	Multivariate approaches for SERS data analysis in clinical applications	395
	Duo Lin, Sufang Qiu, Yang Chen, Shangyuan Feng and Haishan Zeng	
11.1	Introduction	395
11.2	Data analysis for label-free surface-enhanced Raman spectroscopy measurements	396
11.2.1	Unsupervised data analysis and practical applications	396

11.2.2 Supervised data analysis and practical applications 404

11.3 Additional applications in labeling SERS measurements 418

11.3.1 Practical applications of unsupervised analysis 418

11.3.2 Practical applications of supervised data analysis 423

11.4 Concluding remarks 424

References 425

Index 433