

Contents

About the Editors *XVII*
Series Editors Preface *XIX*
Preface *XXI*
List of Contributors *XXV*

- 1 High-Speed Microfluidic Manipulation of Cells 1**
Aram J. Chung and Soojung Claire Hur
- 1.1 Introduction 1
 1.2 Direct Cell Manipulation 3
 1.2.1 Electrical Cell Manipulation 3
 1.2.2 Magnetic Cell Manipulation 4
 1.2.3 Optical Cell Manipulation 4
 1.2.4 Mechanical Cell Manipulation 5
 1.2.4.1 Constriction-Based Cell Manipulation 5
 1.2.4.2 Shear-Induced Cell Manipulation 7
 1.3 Indirect Cell Manipulation 9
 1.3.1 Cell Separation 9
 1.3.1.1 Hydrodynamic (Passive) Cell Separation 13
 1.3.1.2 Nonhydrodynamic (Active) Particle Separation 18
 1.3.2 Cell Alignment (Focusing) 25
 1.3.2.1 Cell Alignment (Focusing) for Flow Cytometry 28
 1.3.2.2 Cell Solution Exchange 29
 1.4 Summary 31
 Acknowledgments 31
 References 31
- 2 Micro and Nano Manipulation and Assembly by Optically Induced Electrokinetics 41**
Fei Fei Wang, Sam Lai, Lianqing Liu, Gwo-Bin Lee, and Wen Jung Li
- 2.1 Introduction 41
 2.2 Optically Induced Electrokinetic (OEK) Forces 45
 2.2.1 Classical Electrokinetic Forces 45
 2.2.1.1 Dielectrophoresis (DEP) 45

2.2.1.2	AC Electroosmosis (ACEO)	46
2.2.1.3	Electrothermal Effects (ET)	47
2.2.1.4	Buoyancy Effects	47
2.2.1.5	Brownian Motion	47
2.2.2	Optically Induced Electrokinetic Forces	48
2.2.2.1	OEK Chip: Operational Principle and Design	48
2.2.2.2	Spectrum-Dependent ODEP Force	53
2.2.2.3	Waveform-Dependent ODEP Force	54
2.3	OEK-Based Manipulation and Assembly	55
2.3.1	Manipulation and Assembly of Nonbiological Materials	55
2.3.2	Biological Entities: Cells and Molecules	60
2.3.3	Manipulation of Fluidic Thin Films	63
2.4	Summary	65
	References	67
3	Manipulation of DNA by Complex Confinement Using Nanofluidic Slits	75
	<i>Elizabeth A. Strychalski and Samuel M. Stavis</i>	
3.1	Introduction	75
3.2	Slitlike Confinement of DNA	78
3.3	Differential Slitlike Confinement of DNA	82
3.4	Experimental Studies	83
3.5	Design of Complex Slitlike Devices	86
3.6	Fabrication of Complex Slitlike Devices	88
3.7	Experimental Conditions	90
3.8	Conclusion	92
	Disclaimer	93
	References	93
4	Microfluidic Approaches for Manipulation and Assembly of One-Dimensional Nanomaterials	97
	<i>Shaolin Zhou, Qiuquan Guo, and Jun Yang</i>	
4.1	Introduction	97
4.2	Microfluidic Assembly	99
4.2.1	Hydrodynamic Focusing	100
4.2.1.1	Concept and Mechanism	100
4.2.1.2	2D and 3D Hierarchy	101
4.2.1.3	Symmetrical and Asymmetrical Behavior	103
4.2.2	HF-Based NW Assembly	104
4.2.2.1	The Principle	104
4.2.2.2	Device Design and Fabrication	105
4.2.2.3	NW Assembly by Symmetrical Hydrodynamic Focusing	107
4.2.2.4	NW Assembly by Asymmetrical Hydrodynamic Focusing	108
4.3	Summary	112
	References	113

- 5 Optically Assisted and Dielectrophoretical Manipulation of Cells and Molecules on Microfluidic Platforms 119**
Yen-Heng Lin and Gwo-Bin Lee
- 5.1 Introduction 119
- 5.2 Operating Principle and Fundamental Physics of the ODEP Platform 122
- 5.2.1 ODEP Force 122
- 5.2.2 Optically Induced ACEO Flow 123
- 5.2.3 Electrothermal (ET) Force 125
- 5.2.4 Experimental Setup of an ODEP Platform 126
- 5.2.4.1 Light Source 126
- 5.2.4.2 Materials of the Photoconductive Layer 127
- 5.3 Applications of the ODEP Platform 129
- 5.3.1 Cell Manipulation 129
- 5.3.2 Cell Separation 130
- 5.3.3 Cell Rotation 130
- 5.3.4 Cell Electroporation 131
- 5.3.5 Cell Lysis 131
- 5.3.6 Manipulation of Micro- or Nanoscale Objects 132
- 5.3.7 Manipulation of Molecules 134
- 5.3.8 Droplet Manipulation 135
- 5.4 Conclusion 136
- References 137
- 6 On-Chip Microrobot Driven by Permanent Magnets for Biomedical Applications 141**
Masaya Hagiwara, Tomohiro Kawahara, and Fumihito Arai
- 6.1 On-Chip Microrobot 141
- 6.2 Characteristics of Microrobot Actuated by Permanent Magnet 142
- 6.3 Friction Reduction for On-Chip Robot 144
- 6.3.1 Friction Reduction by Drive Unit 144
- 6.3.2 Friction Reduction by Ultrasonic Vibrations 146
- 6.3.3 Experimental Evaluations of MMT 146
- 6.3.3.1 Positioning Accuracy Evaluation 146
- 6.3.3.2 Output Force Evaluation 149
- 6.4 Fluid Friction Reduction for On-Chip Robot 150
- 6.4.1 Fluid Friction Reduction by Riblet Surface 150
- 6.4.2 Principle of Fluid Friction Reduction Using Riblet Surface 150
- 6.4.3 Optimal Design of Riblet to Minimize the Fluid Friction 152
- 6.4.4 Fluid Force Analysis on MMT with Riblet Surface 153
- 6.4.5 Fabrication Process of MMT with Riblet Surface Using Si–Ni Composite Structure 156
- 6.4.6 Evaluation of Si–Ni Composite MMT with Optimal Riblet 158
- 6.5 Applications of On-Chip Robot to Cell Manipulations 160
- 6.5.1 Oocyte Enucleation 160

6.5.2	Multichannel Sorting	162
6.5.3	Evaluation of Effect of Mechanical Stimulation on Microorganisms	162
6.6	Summary	165
	References	166
7	Silicon Nanotweezers for Molecules and Cells Manipulation and Characterization	169
	<i>Dominique Collard, Nicolas Lafitte, Hervé Guillou, Momoko Kumemura, Laurent Jalabert, and Hiroyuki Fujita</i>	
7.1	Introduction	169
7.2	SNT Operation and Design	170
7.2.1	Design	170
7.2.1.1	Electrostatic Actuation	171
7.2.1.2	Mechanical Structure	171
7.2.1.3	Capacitive Sensor	173
7.2.2	Operation	174
7.2.2.1	Instrumentation	174
7.2.2.2	Characterization	175
7.2.2.3	Modeling	176
7.3	SNT Process	177
7.3.1	MEMS Fabrication versus the Design Constrains and User Applications	177
7.3.2	Sharp Tip Single Actuator SNT Process Flow	178
7.3.2.1	Nitride Deposition	178
7.3.2.2	Defining Crystallographic Alignment Structures	178
7.3.2.3	Photolithography (Level 1) – Nitride Patterning for LOCOS	179
7.3.2.4	Photolithography (Level 2) – Sensors and Actuators	179
7.3.2.5	DRIE Front Side	180
7.3.2.6	Sharp Tip Fabrication and Gap Control	181
7.3.2.7	Photolithography (Level 3) and Rearside DRIE	182
7.3.2.8	Releasing in Vapor HF	182
7.3.3	Concluding Remarks on the Silicon Nanotweezers Microfabrication	183
7.4	DNA Trapping and Enzymatic Reaction Monitoring	183
7.5	Cell Trapping and Characterization	186
7.5.1	Introducing Remarks	186
7.5.2	Specific Issues	187
7.5.3	Design of SNT	187
7.5.4	Instrumentation	189
7.5.5	Experimental Platform	190
7.5.6	Cells in Suspension	190
7.5.7	Spread Cells	192
7.5.8	Cell Differentiation	193

7.5.9	Concluding Remarks for Cell Characterization with SNT	194
7.6	General Concluding Remarks and Perspectives	194
	Acknowledgments	196
	References	196
8	Miniaturized Untethered Tools for Surgery	201
	<i>Evin Gultepe, Qianru Jin, Andrew Choi, Alex Abramson, and David H. Gracias</i>	
8.1	Introduction	201
8.2	Macroscale Untethered Surgical Tools	203
8.2.1	Localization and Locomotion without Tethers	204
8.2.1.1	Localization	204
8.2.1.2	Locomotion	206
8.2.2	Powering and Activating a Small Machine	207
8.2.2.1	Stored Chemical Energy	207
8.2.2.2	Stored Mechanical Energy	208
8.2.2.3	External Magnetic Field	208
8.2.2.4	Other Sources of Energy	209
8.3	Microscale Untethered Surgical Tools	210
8.3.1	Applications	210
8.3.1.1	Angioplasty	210
8.3.1.2	Surgical Wound Closure	212
8.3.1.3	Biopsy	213
8.3.1.4	Micromanipulation	214
8.3.2	Locomotion	214
8.3.2.1	Magnetic Force	215
8.3.2.2	Electromechanical	217
8.3.2.3	Optical Tweezers	218
8.3.2.4	Biologic Tissue Powered	219
8.4	Nanoscale Untethered Surgical Tools	219
8.4.1	Fuel-Driven Motion	222
8.4.2	Magnetic Field-Driven Motion	223
8.4.3	Acoustic Wave-Driven Motion	225
8.4.4	Light-Driven Motion	226
8.4.5	Nano-Bio Hybrid Systems	227
8.4.6	Artificial Molecular Machines	227
8.5	Conclusion	228
	Acknowledgments	229
	References	229
9	Single-Chip Scanning Probe Microscopes	235
	<i>Neil Sarkar and Raafat R. Mansour</i>	
9.1	Scanning Probe Microscopy	237
9.2	The Role of MEMS in SPM	239
9.3	CMOS–MEMS Manufacturing Processes Applied to sc-SPMs	240

9.4	Modeling and Design of sc-SPMs	242
9.4.1	Electrothermal Model of Self-Heated Resistor	245
9.4.2	Electrothermal Model of Vertical Actuator	247
9.4.3	Electro-Thermo-Mechanical Model	248
9.5	Imaging Results	250
9.6	Conclusion	254
	References	254
10	Untethered Magnetic Micromanipulation	259
	<i>Eric Diller and Metin Sitti</i>	
10.1	Physics of Micromanipulation	260
10.2	Sliding Friction and Surface Adhesion	260
10.2.1	Adhesion	260
10.2.1.1	van der Waals Forces	262
10.2.2	Sliding Friction	263
10.3	Fluid Dynamics Effects	264
10.3.1	Viscous Drag on a Sphere	265
10.4	Magnetic Microrobot Actuation	266
10.5	Locomotion Techniques	266
10.5.1	Motion in Two Dimensions	267
10.5.2	Motion in Three Dimensions	267
10.5.3	Magnetic Actuation Systems	268
10.5.4	Special Coil Arrangements	269
10.6	Manipulation Techniques	271
10.6.1	Contact Micromanipulation	271
10.6.1.1	Direct Pushing	271
10.6.1.2	Grasping Manipulation	274
10.6.2	Noncontact Manipulation	275
10.6.2.1	Translation	276
10.6.2.2	Rotation	277
10.6.2.3	Parallel Manipulation	279
10.6.3	Mobile Microrobotics Competition	279
10.7	Conclusions and Prospects	280
	References	281
11	Microrobotic Tools for Plant Biology	283
	<i>Dimitrios Felekis, Hannes Vogler, Ueli Grossniklaus, and Bradley J. Nelson</i>	
11.1	Why Do We Need a Mechanical Understanding of the Plant Growth Mechanism?	283
11.2	Microrobotic Platforms for Plant Mechanics	285
11.2.1	The Cellular Force Microscope	286
11.2.1.1	Force Sensing Technology	286
11.2.1.2	Positioning System	288
11.2.1.3	Imaging System and Interface	289

- 11.2.2 Real-Time CFM 290
- 11.2.2.1 Positioning System 290
- 11.2.2.2 Data Acquisition 291
- 11.2.2.3 Automated Cell Selection and Positioning 292
- 11.3 Biomechanical and Morphological Characterization of Living Cells 294
- 11.3.1 Cell Wall Apparent Stiffness 295
- 11.3.2 3D Stiffness and Topography Maps 299
- 11.3.3 Real-Time Intracellular Imaging During Mechanical Stimulation 301
- 11.4 Conclusions 302
- References 303

- 12 **Magnetotactic Bacteria for the Manipulation and Transport of Micro- and Nanometer-Sized Objects 307**
Sylvain Martel
- 12.1 Introduction 307
- 12.2 Magnetotactic Bacteria 308
- 12.3 Component Sizes and Related Manipulation Approaches 310
- 12.3.1 Transport and Manipulation of MS Components 311
- 12.3.2 Transport and Manipulation of AE Components 314
- 12.3.3 Transport and Manipulation of ML Components 314
- 12.4 Conclusions and Discussion 317
- References 318

- 13 **Stiffness and Kinematic Analysis of a Novel Compliant Parallel Micromanipulator for Biomedical Manipulation 319**
Xiao Xiao and Yangmin Li
- 13.1 Introduction 319
- 13.2 Design of the Micromanipulator 320
- 13.3 Stiffness Modeling of the Micromanipulator 322
- 13.3.1 Stiffness Matrix of the Flexure Element 323
- 13.3.2 Stiffness Modeling of the Compliant P Module 324
- 13.3.3 Stiffness Modeling of the Compliant 4S Module 325
- 13.3.4 Stiffness Modeling of the Compliant P(4S) Chain 327
- 13.3.5 Stiffness Modeling of the Complete Mechanism 327
- 13.3.6 Model Validation Based on FEA 329
- 13.4 Kinematics Modeling of the Micromanipulator 333
- 13.5 Conclusion 336
- References 337

- 14 **Robotic Micromanipulation of Cells and Small Organisms 339**
Xianke Dong, Wes Johnson, Yu Sun, and Xinyu Liu
- 14.1 Introduction 339
- 14.2 Robotic Microinjection of Cells and Small Organisms 340

14.2.1	Robotic Cell Injection	340
14.2.1.1	Cell Immobilization Methods	343
14.2.1.2	Image Processing and Computer Vision Techniques	344
14.2.1.3	Control System Design	345
14.2.1.4	Force Sensing and Control	347
14.2.1.5	Experimental Validation of Injection Success and Survival Rates	349
14.2.1.6	Parallel Cell Injection	350
14.2.2	Robotic Injection of <i>Caenorhabditis elegans</i>	350
14.3	Robotic Transfer of Biosamples	351
14.3.1	Pipette-Based Cell Transfer	351
14.3.2	Microgripper/Microhand-Based Cell Transfer	352
14.3.3	Microrobot-Based Cell Transfer	354
14.3.4	Laser Trapping-Based Cell Transfer	355
14.4	Robot-Assisted Mechanical Characterization of Cells	357
14.4.1	MEMS-Based Cell Characterization	357
14.4.2	Laser Trapping-Based Cell Characterization	358
14.4.3	Atomic Force Microscopy (AFM)-Based Cell Characterization	359
14.4.4	Micropipette Aspiration	359
14.5	Conclusion	360
	References	361
15	Industrial Tools for Micromanipulation	369
	<i>Michaël Gauthier, Cédric Clévy, David Hériban, and Pasi Kallio</i>	
15.1	Introduction	369
15.2	Microrobotics for Scientific Instrumentation	371
15.2.1	MEMS Mechanical Testing	371
15.2.2	Mechanical Testing of Fibrous Micro- and NanoScale Materials	372
15.2.3	Mobile Microrobots for Testing	375
15.3	Microrobotics for Microassembly	376
15.3.1	Microassembly of Micromechanisms	377
15.3.1.1	Microgrippers	379
15.3.1.2	High-Resolution Vision System	380
15.3.1.3	Integrated Assembly Platform	381
15.3.2	Microassembly in MEMS and MOEMS Industries	382
15.3.2.1	Thin Die Packaging	383
15.3.2.2	Flexible MOEMS Extreme Assembly	384
15.4	Future Challenges	387
15.4.1	Current Opportunities	387
15.4.2	Future Opportunity	388
15.4.3	Barriers to Market	388

- 15.4.4 Key Market Data 389
- References 389

- 16 **Robot-Aided Micromanipulation of Biological Cells with Integrated Optical Tweezers and Microfluidic Chip 393**
Xiaolin Wang, Shuxun Chen, and Dong Sun
- 16.1 Introduction 393
- 16.2 Cell Micromanipulation System with Optical Tweezers and Microfluidic Chip 395
- 16.3 Enhanced Cell Sorting Strategy 396
- 16.3.1 Operation Principle 396
- 16.3.2 Microfluidic Chip Design 397
- 16.3.3 Cell Transportation by Optical Tweezers 398
- 16.3.4 Experimental Results and Discussion 400
- 16.3.4.1 Isolation of Yeast Cells 400
- 16.3.4.2 Isolation of hESCs 402
- 16.3.4.3 Discussion 403
- 16.4 Novel Cell Manipulation Tool 404
- 16.4.1 Operation Principle 404
- 16.4.2 Microwell Array-Based Microfluidic Chip Design 405
- 16.4.3 Chip Preparation and Fluid Operation 406
- 16.4.4 Experimental Results and Discussion 407
- 16.4.4.1 Cell Levitation from Microwell 407
- 16.4.4.2 Cell Assembly by Multiple Optical Traps 408
- 16.4.4.3 Automated Cell Transportation and Deposition 408
- 16.4.4.4 Isolation and Deposition on hESCs and Yeast Cells 410
- 16.4.4.5 Quantification of the Experimental Results 411
- 16.4.4.6 Discussion 413
- 16.5 Conclusion 414
- References 415

- 17 **Investigating the Molecular Specific Interactions on Cell Surface Using Atomic Force Microscopy 417**
Mi Li, Lianqing Liu, Ning Xi, and Yuechao Wang
- 17.1 Background 417
- 17.2 Single-Molecule Force Spectroscopy 420
- 17.3 Force Spectroscopy of Molecular Interactions on Tumor Cells from Patients 423
- 17.4 Mapping the Distribution of Membrane Proteins on Tumor Cells 430
- 17.5 Summary 435
- Acknowledgments 436
- References 436

18	Flexible Robotic AFM-Based System for Manipulation and Characterization of Micro- and Nano-Objects 441 <i>Hui Xie and Stéphane Régnier</i>
18.1	AFM-Based Flexible Robotic System for Micro- or Nanomanipulation 444
18.1.1	The AFM-Based Flexible Robotic System 444
18.1.1.1	The Flexible Robotic Setup 444
18.1.1.2	Force Sensing during Pick-and-Place 444
18.1.2	Experimental Results 446
18.1.2.1	3D Micromanipulation Robotic System 446
18.1.2.2	3D Nanomanipulation Robotic System 449
18.1.3	Conclusion 453
18.2	In situ Peeling of 1D Nanostructures Using a Dual-Probe Nanotweezer 453
18.2.1	Methods 453
18.2.2	Results and Discussion 457
18.2.3	Conclusion 457
18.3	In situ Quantification of Living Cell Adhesion Forces: Single-Cell Force Spectroscopy with a Nanotweezer 459
18.3.1	Materials and Methods 459
18.3.1.1	Nanotweezer Setup 459
18.3.1.2	Cell Cultivation and Sample Preparation 461
18.3.1.3	Nanotweezer Preparation 461
18.3.2	Protocol of the Adhesion Force Measurement 462
18.3.3	Clamping Detection during Cell Grasping 464
18.3.3.1	Cell Release 466
18.3.4	Experimental Results 466
18.3.4.1	Cell–Substrate Adhesion Force Measurement 466
18.3.4.2	Cell–Cell Adhesion Force Measurement 469
18.3.5	Discussion 470
18.3.6	Conclusion 471
18.4	Conclusion and Future Directions 471 References 472
19	Nanorobotic Manipulation of Helical Nanostructures 477 <i>Lixin Dong, Li Zhang, Miao Yu, and Bradley J. Nelson</i>
19.1	Introduction 477
19.2	Nanorobotic Manipulation Tools and Processes 479
19.2.1	Nanomanipulators and Tools 479
19.2.2	Nanorobotic Manipulation Processes 480
19.3	Characterization of Helical Nanobelts 482
19.3.1	Axial Pulling of Rolled-Up Helical Nanostructures 483
19.3.2	Lateral Bending and Local Buckling of a Rolled-Up SiGe/Si Microtube 483
19.3.3	Axial Buckling of Rolled-Up SiGe/Si Microtubes 485

19.3.4	Tangential Unrolling of a Rolled-Up Si/Cr Ring	488
19.3.5	Radial Stretching of a Si/Cr Nanoring	489
19.4	Applications	492
19.4.1	Typical Configurations of NEMS	492
19.4.2	Motion Converters	492
19.4.2.1	Design of Motion Converters	494
19.4.2.2	Displacement Conversion	495
19.4.2.3	Load Conversion	497
19.4.2.4	Application in 3D Microscopy	498
19.5	Summary	500
	References	501
20	Automated Micro- and Nanohandling Inside the Scanning Electron Microscope	505
	<i>Malte Bartenwerfer, Sören Zimmermann, Tobias Tiemerding, Manuel Mikczinski, and Sergej Fatikow</i>	
20.1	Introduction and Motivation	505
20.1.1	SEM-Based Manipulation	506
20.2	State of the Art	508
20.2.1	The Scanning Electron Microscope as Fundamental Tool	508
20.2.2	Conditions for Automation on the Micro- and Nanoscales	509
20.3	Automation Environment	511
20.3.1	Robotic Setup	511
20.3.1.1	Dedicated Setups	511
20.3.1.2	Modular Setups	512
20.3.2	Control Environment	514
20.3.2.1	OFFIS Automation Framework	514
20.4	Case Studies	517
20.4.1	Manipulation and Automation Overview	517
20.4.1.1	High-Speed Object Tracking Inside the SEM	519
20.4.2	Assembly of Building Blocks: NanoBits	521
20.4.2.1	Assembly Environment and Tools	521
20.4.3	Handling of Colloidal Nanoparticles	524
20.4.4	Measuring the Transverse Fiber Compression	526
20.5	Outlook	530
20.5.1	Future Developments	530
20.5.2	Software and Automation	530
	Acknowledgments	531
	References	531
21	Manipulation of Biological Cells under ESEM and Microfluidic Systems	537
	<i>Toshio Fukuda, Masahiro Nakajima, Masaru Takeuchi, and Mohd Ridzuan Ahmad</i>	
21.1	Introduction	537

21.2	ESEM-Nanomanipulation System	538
21.3	ESEM Observation of Single Cells	540
21.4	Manipulation of Biological Cells under ESEM	541
21.4.1	Cell Viability Detection Using Dual Nanoprobe	541
21.4.2	Preparation of Dead Cell Colonies of W303 Cells	543
21.4.3	Fabrication of the Dual Nanoprobe	544
21.4.4	Electrical Measurement Setup	545
21.4.5	Experimental Results and Discussions	546
21.4.5.1	Single-Cell Viability Assessment by Electrical Measurement under HV Mode	547
21.4.5.2	Single-Cell Viability Assessment by Electrical Measurement under ESEM Mode	548
21.5	Manipulation of Biological Cells under Microfluidics	549
21.5.1	Nanoliters Discharge/Suction by Thermoresponsive Polymer Actuated Probe	549
21.5.2	Fabrication of TPA Probe	550
21.5.3	Solution Discharge by TPA Probe	552
21.5.4	Suction and Discharge of Micro-Object by TPA Probe Inside Semiclosed Microchip	553
21.5.4.1	Semiclosed Microchip	553
21.5.4.2	Suction and Discharge of Microbead by TPA Probe Inside Semiclosed Microchip	554
21.5.4.3	Cell Suction by TPA Probe Inside Semiclosed Microchip	556
21.6	Conclusion	556
	References	557

Index 559