

# Contents

Foreword	xv
Preface	xvii
<b>CHAPTER 1</b>	
Introduction to Clinical Optical Imaging	1
1.1 Introduction	1
1.2 Tissue Optics	2
1.2.1 Scattering	2
1.2.2 Raman Scattering	3
1.2.3 Absorption	3
1.2.4 Fluorescence	4
1.3 Light Propagation	6
1.3.1 Fundamentals	6
1.3.2 Forward Model	7
1.4 Multimodality Imaging	9
1.4.1 A Brief History of Clinical Multimodality Imaging	9
1.4.2 Multimodality Optical Imaging	10
1.5 Conclusions	13
References	13
<b>CHAPTER 2</b>	
In Vivo Microscopy	19
2.1 Introduction	19
2.2 Confocal Microscopy	20
2.3 Endoscope-Compatible Systems	20
2.4 MKT Cellvizio-GI	23
2.5 Dual-Axes Confocal Microscope	25
2.6 Molecular Imaging	27
References	30
<b>CHAPTER 3</b>	
Endoscopy	33
3.1 Introduction	33
3.2 Point-Probe Spectroscopy Techniques	33
3.2.1 Scattering Spectroscopy	34
3.2.2 Fluorescence Spectroscopy	36
3.2.3 Raman Spectroscopy	38

3.2.4	Multimodality Spectroscopy	38
3.3	Wide-Field Imaging	39
3.3.1	Fluorescence Imaging	39
3.3.2	Molecular Imaging	41
3.3.3	Chromoendoscopy	42
3.3.4	Narrowband Imaging	43
3.3.5	Multimodality Wide-Field Imaging	43
3.4	Cross-Sectional Imaging	44
3.4.1	Endoscopic Optical Coherence Tomography	44
3.4.2	Ultrahigh-Resolution OCT (UHROCT)	45
3.4.3	Three-Dimensional OCT	46
3.4.4	Multimodality Imaging with OCT	47
3.5	Summary	51
	Acknowledgments	51
	References	51
<b>CHAPTER 4</b>		
	Diffuse Optical Techniques: Instrumentation	59
4.1	Introduction: Deterministic "Diffuse" Detection of Probabilistic Photon Propagation	59
4.2	Methods of Differentiating the Origin of Diffuse Photons	60
4.2.1	The Source-Encoding Requirement in DOT	61
4.2.2	Methods of Source Encoding and Detector Decoding for Diffuse Optical Tomography	62
4.3	Techniques of Decoupling the Absorption and Scattering Contributions to the Photon Remission	65
4.3.1	Time-Domain Detection	66
4.3.2	Frequency-Domain Detection	68
4.3.3	Continuous-Wave Detection	70
4.4	Principles of Determining the Heterogeneity of Optical Properties	70
4.4.1	Tomographic Image Reconstruction and Prior Utilization	70
4.4.2	Diffuse Optical Tomography Imaging in the Context of Multimodality Imaging	73
4.5	Novel Approaches in Instrumentation of Diffuse Optical Tomography: Source Spectral Encoding	76
4.5.1	Discrete Spectral Encoding by Use of Multiple Laser Diodes	76
4.5.2	Imaging Examples of Spectral-Encoding Rapid NIR Tomography	78
4.5.3	Spread Spectral Encoding by Use of Single Wideband Light Source	80
4.5.4	Light Sources for Spread Spectral Encoding	81
4.5.5	Characteristics of Spread Spectral Encoding	82
4.5.6	Hemodynamic Imaging by Spread-Spectral-Encoding NIR Tomography	84
4.6	Novel Approaches in Instrumentation of Diffuse Optical Tomography: Transrectal Applicator	85
4.6.1	Transrectal Applicator for Transverse DOT Imaging	86
4.6.2	Transrectal Applicator for Sagittal DOT Imaging	88



4.7	Potential Directions of Instrumentation for Diffuse Optical Measurements	93
4.8	Conclusions	94
	Acknowledgments	94
	References	94

## CHAPTER 5

	Multimodal Diffuse Optical Tomography: Theory	101
5.1	Introduction	101
5.2	Diffuse Optical Tomography	102
	5.2.1 The Forward Problem and Linearization	103
	5.2.2 Inverse Problem	106
5.3	Multimodality Reconstruction: Review of Previous Work	108
5.4	Multimodality Priors and Regularization	111
	5.4.1 Structural Priors	111
	5.4.2 Regularization Using Mutual Information	113
5.5	Conclusions	119
	Acknowledgments	119
	References	120

## CHAPTER 6

	Diffuse Optical Spectroscopy with Magnetic Resonance Imaging	125
6.1	Introduction	125
6.2	Anatomical Imaging	126
6.3	Combining Hemodynamic Measures of MRI and Optical Imaging	128
6.4	MRI-Guided Optical Imaging Reconstruction Techniques	131
6.5	Other MR-Derived Contrast and Optical Imaging	133
6.6	Hardware Challenges to Merging Optical and MRI	134
6.7	Optical/MR Contrast Agents	135
6.8	Outlook for MR-Optical Imaging	136
	References	136

## CHAPTER 7

	Software Platforms for Integration of Diffuse Optical Imaging and Other Modalities	141
7.1	Introduction	141
	7.1.1 A Platform for Diffuse Optical Tomography	141
	7.1.2 A Platform for Diffuse Optical Spectroscopy	142
7.2	Imaging Platform Technologies	143
	7.2.1 Multimodal Imaging Workflow for DOT Applications	143
	7.2.2 3D-DOT/3D-MRI Image-Registration Algorithm	144
	7.2.3 Breast MRI Image Segmentation	151
	7.2.4 Image-Based Guidance Workflow and System for DOS Applications	152
7.3	Computing the Accuracy of a Guidance and Tracking System	153
	7.3.1 Global Accuracy of the System	153
	7.3.2 Motion Tracking	154

7.4	Application to Nonconcurrent MRI and DOT Data of Human Subjects	155
7.5	Conclusion	157
	Acknowledgments	158
	References	158
	Selected Bibliography	162
<b>CHAPTER 8</b>		
	Diffuse Optical Spectroscopy in Breast Cancer: Coregistration with MRI and Predicting Response to Neoadjuvant Chemotherapy	163
8.1	Introduction	163
8.2	Coregistration with MRI	164
	8.2.1 Materials and Methods	164
	8.2.2 Results	167
	8.2.3 Discussion	175
8.3	Monitoring and Predicting Response to Breast Cancer Neoadjuvant Chemotherapy	176
	8.3.1 Materials and Methods	176
	8.3.2 Results	177
	8.3.3 Discussion	180
8.4	Summary and Conclusions	181
	Acknowledgments	182
	References	182
<b>CHAPTER 9</b>		
	Optical Imaging and X-Ray Imaging	185
9.1	Introduction	185
	9.1.1 Current Clinical Approach to Breast Cancer Screening and Diagnosis	185
	9.1.2 The Importance of Fusing Function and Structural Information	186
	9.1.3 Recent Advances in DOT for Imaging Breast Cancer	187
9.2	Instrumentation and Methods	188
	9.2.1 Tomographic Optical Breast-Imaging System and Tomosynthesis	188
	9.2.2 3D Forward Modeling and Nonlinear Image Reconstruction	190
	9.2.3 Simultaneous Image Reconstruction with Calibration Coefficient Estimation	190
	9.2.4 Utilizing Spectral Prior and Best Linear Unbiased Estimator	191
	9.2.5 Utilizing Spatial Prior from Tomosynthesis Image	192
9.3	Clinical Trial of TOBI/DBT Imaging System	192
	9.3.1 Image Reconstruction of Healthy Breasts	193
	9.3.2 Imaging Breasts with Tumors or Benign Lesions	193
	9.3.3 Region-of-Interest Analysis	194
9.4	Dynamic Imaging of Breast Under Mechanical Compression	194
	9.4.1 Experiment Setup	194
	9.4.2 Tissue Dynamic from Healthy Subjects	195

9.4.3	Contact Pressure Map Under Compression	197
9.5	Conclusions	198
	References	199
<b>CHAPTER 10</b>		
	Diffuse Optical Imaging and PET Imaging	205
10.1	Introduction	205
10.2	Positron Emission Tomography (PET)	207
10.2.1	PET Fundamentals	207
10.2.2	PET Image Reconstruction	208
10.2.3	PET Instrumentation	209
10.3	Diffuse Optical Imaging (DOI)	210
10.3.1	DOI Instrumentation	210
10.3.2	DOI Image Reconstruction	211
10.4	Fluorescence Diffuse Optical Imaging (FDOI)	212
10.5	Clinical Observations	214
10.5.1	Whole-Body PET and DOI	214
10.5.2	Breast-Only PET and DOI	216
10.5.3	ICG Fluorescence	216
10.6	Summary	219
	Acknowledgments	220
	References	220
<b>CHAPTER 11</b>		
	Photodynamic Therapy	225
11.1	Introduction	225
11.2	Basics of PDT	227
11.3	Superficial Applications	230
11.4	PDT in Body Cavities	231
11.5	PDT for Solid Tumors	233
11.6	Delivery and Monitoring of PDT	235
11.7	The Future of PDT and Imaging	236
11.8	Acknowledgments	236
	References	236
<b>CHAPTER 12</b>		
	Optical Phantoms for Multimodality Imaging	241
12.1	Introduction	241
12.2	Absorption and Scatter Phantom Composition	242
12.3	Typical Tissue Phantoms for Multimodal and Optical Imaging	245
12.3.1	Hydrogel-Based Phantoms	245
12.3.2	Polyester Resin and RTV Silicone Phantoms	249
12.3.3	Aqueous Suspension Phantoms	251
12.4	Conclusions	253
	Acknowledgments	254
	References	254

**CHAPTER 13**

Intraoperative Near-Infrared Fluorescent Imaging Exogenous Fluorescence Contrast Agents	259
13.1 Introduction	259
13.2 Unmet Medical Needs Addressed by Intraoperative NIR Fluorescence Imaging	259
13.2.1 Improving Long-Term Efficacy of Primary Treatment	260
13.2.2 Reducing the Rate of Complications	261
13.3 Imaging Considerations	262
13.3.1 Contrast Media	262
13.3.2 Tissue Penetration Depth	263
13.3.3 Autofluorescence	265
13.3.4 Optical Design Considerations	265
13.3.5 Excitation	267
13.3.6 Collection Optics and Emission Filtering	267
13.3.7 Detectors	268
13.4 Future Outlook	268
References	269

**CHAPTER 14**

Clinical Studies in Optical Imaging: An Industry Perspective	275
14.1 Introduction	275
14.2 Breast Cancer	276
14.3 Optical Breast-Imaging Technology	277
14.4 Development Process	277
14.4.1 Product Definition	278
14.4.2 Clinical Indication	279
14.4.3 Target Markets	280
14.4.4 Regulatory Risk Classification	282
14.4.5 General Device Description	282
14.4.6 Design Control	285
14.5 Clinical Trials and Results	286
14.5.1 Clinical Plan	286
14.5.2 Pilot Studies	286
14.5.3 Tissue-Characterization Trials	287
14.6 Conclusions	294
Acknowledgments	294
References	295

**CHAPTER 15**

Regulation and Regulatory Science for Optical Imaging	299
15.1 Introduction	299
15.2 Fundamental Concepts in Medical Device Regulation	300
15.2.1 Premarket and Postmarket	301
15.2.2 Safety	301
15.2.3 Effectiveness	301
15.2.4 Risk Evaluation	301



15.2.5	Labeling	302
15.2.6	Standards	302
15.3	Medical Device Regulation Throughout the World	302
15.3.1	International Harmonization of Medical Device Regulation	303
15.4	FDA Background	304
15.4.1	FDA Mission	304
15.4.2	FDA History and Authorizing Legislation	304
15.4.3	Organizational Structure of the FDA	305
15.5	Overview of FDA Regulations	305
15.5.1	Classification	307
15.5.2	Early Premarket Interactions	310
15.5.3	Premarket Submissions	311
15.5.4	Postmarket Issues	312
15.5.5	Combination Products and Contrast Agents	313
15.5.6	Regulatory Submission Aids	313
15.5.7	Good Practices	314
15.6	Regulatory Science: Optical Safety Hazards	315
15.6.1	Photochemical Damage	316
15.6.2	Photosensitivity	318
15.6.3	Photothermal Effects	318
15.6.4	Photomechanical Damage	320
15.7	Conclusions	322
	Acknowledgments	322
	References	322

## CHAPTER 16

	Emerging Optical Imaging Technologies: Contrast Agents	327
16.1	Introduction	327
16.2	Optical Probes	328
16.2.1	Fluorophores as Contrast Agents for Optical Imaging	328
16.2.2	Fluorophore Conjugates for Targeting and Activation	330
16.2.3	Fluorescent Nanoparticles	331
16.3	Multimodality Probes for Optical Imaging	332
16.3.1	Probes for Optical Imaging and MRI	332
16.3.2	Probes for Optical Imaging and SPECT/PET	335
16.3.3	Probes for Optical Imaging and Therapy	336
16.4	Summary and Conclusions	337
	References	337

## CHAPTER 17

	Emerging Optical Imaging Techniques: Fluorescence Molecular Tomography and Beyond	343
17.1	Introduction	343
17.2	From Planar Imaging to Tomography	344
17.2.1	Prerequisites	344
17.2.2	Bioluminescence and Fluorescence Imaging	345
17.2.3	Data-Collection Modes	345

17.3	Fluorescence Molecular Tomography	347
17.3.1	Hardware Development	347
17.3.2	Image Reconstruction	349
17.3.3	Intrinsic Resolution Limits	350
17.4	FMT-Derived Imaging Modalities	351
17.4.1	Noncontact FMT	351
17.4.2	Fluorescent Protein Tomography	351
17.4.3	Mesoscopic Fluorescence Tomography	353
17.4.4	Further Developments	354
17.5	Photoacoustic Tomography	355
17.5.1	Photoacoustic Theory	356
17.5.2	Combined FMT-PAT Imaging	357
17.6	Summary	357
	References	359
<b>CHAPTER 18</b>		
	From Benchtop to Boardroom: Staying Market Focused	363
18.1	Identify the Market	363
18.2	Technology Alone Has Little Value	364
18.3	Find a Business Mentor	365
18.4	Tell a Story Using the Right Terms	365
18.5	Focus Is the Key	366
18.6	Build Value	367
18.7	Conclusions	367
	References	368
	About the Editors	369
	List of Contributors	371
	Index	375