

# Contents

<i>Contributors</i>	xiii
<i>Preface</i>	xv
<b>1. Preamble</b>	<b>1</b>
<i>J Wu and W Nyborg</i>	
References . . . . .	3
<b>2. Mechanisms for Bioeffects of Ultrasound Relevant to Therapeutic Applications</b>	<b>5</b>
<i>W L Nyborg</i>	
1 Introduction . . . . .	5
1.1 General considerations . . . . .	5
1.2 Traveling plane wave . . . . .	7
2 Thermal Considerations . . . . .	10
2.1 Temperature distributions: One dimension . . . . .	10
2.2 Acoustic pressure distributions:	
Three dimensions . . . . .	14
2.2.1 Piston in a baffle . . . . .	14
2.2.2 Small source . . . . .	15
2.2.3 Acoustic field on the axis of a piston source . . . . .	16
2.2.4 Other situations . . . . .	17
2.3 Biological effects of heat: Reaction kinetics . . . . .	19
3 Acoustic Radiation Force and Related Topics . . . . .	20
3.1 Intensity and power . . . . .	21

3.2	Radiation force and radiation pressure . . . . .	21
3.3	Radiation force on small particles . . . . .	24
4	Acoustic Streaming and Acoustic Radiation Torque . . . . .	28
4.1	Quartz-wind streaming . . . . .	28
4.2	Near-boundary streaming . . . . .	29
5	Activation of Gas Bodies; Cavitation; Bubbles . . . . .	32
5.1	Bubble dynamics; moderate amplitudes . . . . .	33
5.2	Heating . . . . .	37
5.3	Bubble growth . . . . .	37
5.4	Radiation force on a small gas body in a plane traveling wave . . . . .	38
5.5	Radiation force on a small gas body in a plane standing wave . . . . .	41
5.6	Radiation force between two small gas bodies in a sound field . . . . .	42
5.7	Radiation force on a particle near a small gas body . . . . .	42
5.8	Role of gas bodies in acoustic streaming and microstreaming . . . . .	43
6	Nonlinearity . . . . .	48
6.1	Nonlinear propagation and some of its implications . . . . .	48
6.2	Nonlinear activation of gas bodies; inertial cavitation . . . . .	49
6.3	Techniques for detection of small gas-filled cavities and monitoring of cavitation activity . . . . .	52
6.4	Bioeffects resulting from activation of gas bodies, including inertial cavitation . . . . .	52
7	Conclusions . . . . .	57
	References . . . . .	59

### **3. Ultrasound-Mediated Gene Therapy 69**

*D L Miller*

1	Introduction . . . . .	70
2	Biophysical Foundations . . . . .	73

2.1	Bioeffects of ultrasound . . . . .	73
2.2	Methods for ultrasound-mediated gene transfer . . . . .	75
2.2.1	Ultrasound exposure systems . . . . .	75
2.2.2	Means of cavitation enhancement . . . . .	78
2.2.3	Genetic material configuration . . . . .	79
2.3	Basic <i>in vitro</i> research . . . . .	81
2.3.1	Sonoporation . . . . .	81
2.3.2	Transfection . . . . .	85
2.3.3	Relevance of <i>in vitro</i> tests to <i>in vivo</i> conditions . . . . .	91
3	Ultrasound-mediated Gene Transfer <i>In Vivo</i> . . . . .	92
3.1	Cancer . . . . .	93
3.2	Endovascular tissue . . . . .	97
3.3	Skeletal muscle . . . . .	98
3.4	Myocardium . . . . .	100
3.5	Other potential applications . . . . .	103
4	Ultrasound-Mediated Gene Therapy . . . . .	105
4.1	Cancer . . . . .	106
4.2	Muscular ischemia . . . . .	109
4.3	Myocardial infarction . . . . .	110
4.4	Vascular restenosis . . . . .	112
4.5	Transplant rejection . . . . .	113
4.6	Renal fibrosis . . . . .	115
4.7	Dental injury . . . . .	116
5	Problems and Prospects . . . . .	116
5.1	Problems . . . . .	116
5.2	Prospects . . . . .	118
5.3	Conclusion . . . . .	121
	References . . . . .	122

**4. Emerging Technologies Using Ultrasound for Drug Delivery 131**

*K Tachibana and S Tachibana*

1	Introduction . . . . .	132
2	Historical Background . . . . .	134

3	Stroke Therapy . . . . .	139
4	Microbubbles . . . . .	145
5	Regenerative Medicine . . . . .	149
6	Breakthrough in Developmental Research . . . . .	152
7	Sonodynamic Therapy . . . . .	155
8	Molecular Imaging and Therapy . . . . .	158
9	Conclusions and Outlook . . . . .	161
	References . . . . .	161

**5. MRI-guided Focused Ultrasound for Local Tissue Ablation and Other Image-guided Interventions 167**

*K Hynynen and N McDannold*

1	Introduction . . . . .	167
2	MRI for Guidance, Monitoring and Control of FUS . . . . .	169
3	Clinical MRI-guided Focused Ultrasound Surgery Devices . . . . .	173
	3.1 Fixed focus devices . . . . .	173
	3.2 A phased array system for uterine fibroid and breast cancer treatments . . . . .	175
	3.3 Brain treatments . . . . .	179
4	Pre-clinical Research of MRI-guided Interventions . . . . .	183
	4.1 Intracavitary applicators . . . . .	183
	4.1.1 Prostate treatments . . . . .	183
	4.1.2 Trans-esophageal focused ultrasound ablation . . . . .	185
	4.2 Utilization of cavitation effects . . . . .	185
	4.2.1 Bubble enhanced heating . . . . .	186
	4.2.2 Mechanical destruction of tissue . . . . .	189
	4.3 Vascular effects . . . . .	190
	4.3.1 Blood vessel occlusion . . . . .	190
	4.3.2 Thrombolysis . . . . .	194
	4.3.3 Blood-brain barrier disruption . . . . .	196
	4.4 Gene therapy . . . . .	200
5	Conclusions . . . . .	201
	References . . . . .	201

## **6. Sonoporation, Gene Transfection, Anticancer Drug and Antibody Delivery Using Ultrasound 219**

*J Wu*

1	Introduction . . . . .	219
2	Demonstration of Sonoporation . . . . .	221
3	The Effects of Optison® Concentration . . . . .	222
4	Microstreaming Generated by EMBs Near Cells . . . . .	222
5	Delivery of DNA Using Sonoporation and Electroporation . . . . .	225
5.1	Plasmid DNA preparation . . . . .	225
5.2	Cell preparation . . . . .	226
5.3	Ultrasound exposure and calibration . . . . .	226
5.4	Electroporation procedure . . . . .	228
5.5	Flow cytometer . . . . .	228
5.6	Experimental results . . . . .	228
6	Delivery of Antibodies and Anticancer Drug Using Sonoporation and Electroporation . . . . .	232
6.1	Cell preparation . . . . .	233
6.2	Ultrasound exposure and calibration . . . . .	233
6.3	Flow Cytometer . . . . .	233
6.4	Experimental results and discussion . . . . .	233
6.5	Discussion and summary . . . . .	237
	Appendix . . . . .	239
	References . . . . .	244

## **7. Low-Frequency Sonophoresis: Ultrasound-Mediated Transdermal Drug Delivery 247**

*S Mitragotri*

1	Introduction . . . . .	247
1.1	Avoiding drug degradation in the gastrointestinal tract . . . . .	248
1.2	Better patient compliance . . . . .	248
1.3	Sustained release of the drug can be obtained . . . . .	248
2	Ultrasound in Medical Application . . . . .	249
3	Historical Overview of Sonophoresis . . . . .	251

4	Low-Frequency Sonophoresis . . . . .	252
5	Sonophoresis: Choice of Parameters . . . . .	253
6	Macromolecular Delivery . . . . .	255
	6.1 Peptides and proteins . . . . .	255
	6.2 Low-molecular weight heparin . . . . .	256
	6.3 Oligonucleotides . . . . .	256
	6.4 Vaccines . . . . .	258
7	Transdermal Extraction of Analytes Using Sonophoresis . . . . .	259
8	Mechanism of Low-Frequency Sonophoresis . . . . .	261
9	Synergistic Effect of Ultrasound and Other Mechanism . . . . .	264
	9.1 Ultrasound and chemical enhancers . . . . .	265
	9.2 Ultrasound and iontophoresis . . . . .	265
	9.3 Ultrasound and electroporation . . . . .	266
10	Mathematical Modeling of Sonophoresis . . . . .	267
11	Safety of Low-Frequency Ultrasound . . . . .	270
	References . . . . .	271

## **8. Clinical Applications of High Intensity Focused Ultrasound in the Treatment of Patients with Solid Malignancy 279**

*F Wu*

1	Introduction . . . . .	280
2	History of Extracorporeal HIFU . . . . .	281
3	Mechanism of HIFU Ablation . . . . .	284
4	HIFU Therapeutic Plan . . . . .	286
	4.1 Pre-HIFU planning . . . . .	286
	4.2 Imaging for HIFU planning . . . . .	287
	4.3 Tumor volume localization . . . . .	288
	4.4 Acoustic path for ultrasound energy entry . . . . .	289
	4.5 Ultrasonic properties of overlying tissues . . . . .	290
	4.6 Therapeutic planning using HIFU device . . . . .	291
5	HIFU 3-D Conformal Therapy . . . . .	294
6	Imaging in HIFU . . . . .	299

6.1	Medical images used in HIFU . . . . .	299
6.2	Medical imaging for HIFU planning . . . . .	301
6.3	Medical imaging for HIFU procedure . . . . .	301
6.4	Follow-up imaging for assessment of HIFU ablation . . . . .	304
7	Clinical Applications of Extracorporeal HIFU . . . . .	313
7.1	Purposes of HIFU treatment . . . . .	314
7.2	Anesthesia selection for HIFU procedure . . . . .	315
7.3	HIFU treatment for liver cancer . . . . .	316
7.4	HIFU treatment for breast cancer . . . . .	319
7.5	HIFU treatment for osteosarcoma . . . . .	322
7.6	HIFU treatment for other malignancies . . . . .	324
7.7	Complications of HIFU treatment . . . . .	326
8	Future of HIFU . . . . .	327
	Appendix-Glossary . . . . .	328
	References . . . . .	331

*Index*

341