

# CONTENTS

Contributors	xvii
Preface	xxiii
1. Oncogenetic Trees	1
<i>Aniko Szabo and Kenneth M. Boucher</i>	
1. Introduction . . . . .	1
2. Definitions and Basic Results . . . . .	2
2.1. Description of the Data . . . . .	2
2.2. The Oncogenetic Tree Model . . . . .	3
2.2.1. Error model . . . . .	5
3. Reconstruction . . . . .	5
4. Sample Size Estimation . . . . .	11
5. Parameter Estimation . . . . .	13
6. Example: Renal Carcinoma Development . . . . .	14
7. Properties of the Oncogenetic Tree Estimator: A Simulation Study . . . . .	15
7.1. Simulating Data Based on a Given Tree . . . . .	16
7.2. Probability of Correct Reconstruction . . . . .	16
7.3. Sample Size for High Probability of Reconstruction	17
8. Goodness of Fit . . . . .	19
8.1. Bootstrap Estimate of Reconstruction Confidence .	19
8.2. Analysis of the Stable Portions . . . . .	19
9. Discussion . . . . .	22
References . . . . .	23

2.	Stochastic Multistage Cancer Models: A Fresh Look at an Old Approach	25
	<i>Qi Zheng</i>	
1.	Introduction . . . . .	25
2.	Basic Definitions and Notation . . . . .	26
3.	Mathematical Details . . . . .	32
4.	Concluding Remarks . . . . .	41
	Acknowledgments . . . . .	42
	References . . . . .	42
3.	Cancer Biology, Cancer Models and Some New Approaches to Carcinogenesis	45
	<i>Wai Y. Tan, Chao W. Chen and Li J. Zhang</i>	
1.	Introduction . . . . .	45
2.	Some Recent Cancer Biology for Modeling Carcinogenesis . . . . .	47
2.1.	The Multi-Staging Nature of Carcinogenesis . . . . .	49
2.2.	The Sequential Nature . . . . .	50
2.3.	The Genetic Changes and Cancer Genes . . . . .	53
2.4.	Cell Cycle and Carcinogenesis . . . . .	55
2.5.	Epigenetic and Cancer . . . . .	57
2.6.	Telomere, Immortalization and Cancer . . . . .	60
2.7.	Single Pathway versus Multiple Pathways of Carcinogenesis . . . . .	61
3.	Some General Stochastic Models of Carcinogenesis . . . . .	64
3.1.	The Extended Multi-Event Model of Carcinogenesis . . . . .	64
3.2.	The Mixed Models of Carcinogenesis . . . . .	65
4.	Some New Approaches for Analyzing Stochastic Models of Carcinogenesis . . . . .	66
4.1.	Stochastic Differential Equations . . . . .	67
4.2.	The Probability Distribution of $T(t)$ . . . . .	69
4.3.	Probability Distribution of the State Variables . . . . .	69

5.	A State Space Model for the Extended Multi-Event Model of Carcinogenesis . . . . .	70
5.1.	The Stochastic System Model, the Augmented State Variables and Probability Distribution . . . . .	71
5.2.	The Observation Model and the Probability Distribution of Cancer Incidence . . . . .	72
5.3.	The Posterior Distribution of the Unknown Parameters and State Variables . . . . .	74
5.4.	The Generalized Bayesian Method for Estimating Unknown Parameters and State Variables . . . . .	75
6.	Analysis of British Physician Data of Lung Cancer and Smoking . . . . .	76
7.	Conclusions and Summary . . . . .	83
	Acknowledgments . . . . .	83
	References . . . . .	84
4.	Modeling the Effects of Radiation on Cell Cycle Regulation and Carcinogenesis . . . . .	91
	<i>William D. Hazelton</i>	
1.	Introduction . . . . .	92
1.1.	Multistage Carcinogenesis Models . . . . .	92
1.2.	Analyses of Environmentally Exposed Cohorts . . . . .	93
2.	Modeling Biological Mechanisms . . . . .	95
2.1.	A Combined Cell Cycle and Multistage Clonal Expansion Model . . . . .	95
3.	Summary . . . . .	102
	Acknowledgments . . . . .	103
	References . . . . .	103
	Appendix . . . . .	104
5.	Cancer Models, Ionizing Radiation, and Genomic Instability: A Review . . . . .	109
	<i>Mark P. Little</i>	
1.	Introduction . . . . .	109
2.	Armitage-Doll Multi-Stage Model . . . . .	113

3.	Two-Mutation Model . . . . .	119
4.	Generalized MVK and Multi-Stage Models . . . . .	123
5.	Multiple Pathway Models . . . . .	128
5.1.	Multiple Pathway Models Incorporating Genomic Instability . . . . .	129
6.	Discussion and Conclusions . . . . .	133
	Acknowledgments . . . . .	138
	References . . . . .	138
6.	Distribution of the Sizes of Metastases: Mathematical and Biomedical Considerations . . . . .	149
	<i>Leonid Hanin</i>	
1.	Introduction . . . . .	149
2.	The Model . . . . .	155
2.1.	Tumor Latency . . . . .	155
2.2.	Primary Tumor Growth . . . . .	155
2.3.	Metastasis Formation . . . . .	155
2.4.	Timeline of the Natural History of Metastatic Cancer and Observables . . . . .	156
2.5.	Secondary Metastasis . . . . .	157
2.6.	Metastasis Growth . . . . .	157
2.7.	Metastasis Detection . . . . .	158
2.8.	Effects of Treatment . . . . .	158
3.	Distribution of the Sizes of Detectable Metastases . . . . .	158
4.	Distribution of the Sizes of Detectable Metastases for Exponentially Growing Tumors . . . . .	162
4.1.	Model Specification and Results . . . . .	162
4.2.	Model Identification . . . . .	165
	Acknowledgments . . . . .	167
	References . . . . .	168
7.	Mathematical Models of Cancer and their Relevant Insights . . . . .	173
	<i>Evans Afenya</i>	
1.	Introduction . . . . .	173
2.	Cancer Models . . . . .	176

2.1.	Models of Leukemia . . . . .	177
2.2.	Cell Kinetics . . . . .	195
3.	Cancer Treatment Models . . . . .	200
3.1.	Optimal Control Models . . . . .	201
4.	Parameter Estimation . . . . .	210
5.	Concluding Remarks . . . . .	211
	References . . . . .	213
8.	Major Epigenetic Hypotheses of Carcinogenesis Revisited . . . . .	225
	<i>King-Thom Chung</i>	
1.	Introduction . . . . .	226
2.	Why are Epigenetic Factors Important? . . . . .	230
3.	The Warburg's Hypothesis . . . . .	232
4.	The Linus Pauling Hypothesis: Vitamin C and Cancer . . . . .	233
5.	Szent-Györgyi (Bioelectronic) Hypothesis . . . . .	236
6.	Micronutrients and Cancer . . . . .	238
7.	NAD Deficiency as a Factor in Carcinogenesis . . . . .	242
8.	GAP Junction Intercellular Communication (GJIC) and Cancer . . . . .	251
9.	Viral Infections and Cancer . . . . .	254
10.	Other Epigenetic Hypotheses . . . . .	259
11.	Concluding Remarks and Perspectives . . . . .	262
	Acknowledgments . . . . .	265
	References . . . . .	266
9.	Induction and Repair of DNA Damage Formed by Energetic Electrons and Light Ions . . . . .	291
	<i>Robert D. Stewart and Vladimir A. Semenenko</i>	
1.	Dosimetric Quantities and Units . . . . .	291
1.1.	Absorbed Dose . . . . .	291
1.2.	Linear Energy Transfer (LET) . . . . .	292
1.3.	Microdosimetry . . . . .	294
2.	Induction of DNA Damage . . . . .	297
2.1.	Classification of DNA Damage . . . . .	297
2.2.	Mechanisms . . . . .	297
2.3.	Initial Yield and Characteristics . . . . .	300

3.	Repair of Base Damage and Single-Strand Breaks . . . . .	303
3.1.	Mechanisms . . . . .	303
3.2.	Excision Repair Outcomes and Kinetics . . . . .	304
3.3.	Point Mutations Arising from Base Damage and Single-Strand Breaks . . . . .	307
4.	Repair of Double-Strand Breaks . . . . .	308
4.1.	Mechanisms . . . . .	308
4.2.	Repair Kinetics, Chromosome Aberrations and Small-Scale Mutations . . . . .	310
	Acknowledgments . . . . .	314
	References . . . . .	314
	Appendix . . . . .	319
10.	Radiation-Induced Bystander Effects . . . . .	323
	<i>Linda C. DeVeaux</i>	
1.	Bystander Effects . . . . .	323
1.1.	Introduction . . . . .	323
1.2.	Definition of Bystander Effects . . . . .	325
1.3.	History of Bystander Effects . . . . .	326
1.4.	Bystander Endpoints . . . . .	328
1.5.	Transmission of Signal . . . . .	330
1.6.	Identification of Signal . . . . .	331
1.7.	Status of Sending and Receiving Cells . . . . .	333
1.8.	Dependence on Radiation Type . . . . .	335
1.9.	Bystander Effects and Cancer Risk . . . . .	336
1.10.	Evolutionary Considerations of Bystander Effects . . . . .	336
2.	Summary . . . . .	338
	Acknowledgments . . . . .	338
	References . . . . .	338
11.	A Stochastic Model of Human Colon Cancer Involving Multiple Pathways . . . . .	345
	<i>Wai Y. Tan, Li J. Zhang, Chao W. Chen and J. M. Zhu</i>	
1.	Introduction . . . . .	345
2.	A Brief Summary of Colon Cancer Biology . . . . .	347

2.1.	The LOH Pathway of Human Colon Cancer (The APC- $\beta$ – Catenin – Tcf – myc Pathway) . . .	347
2.2.	The MSI (Micro-Satellite Instability) Pathway of Human Colon Cancer . . . . .	349
3.	The Stochastic Multi-Stage Model of Carcinogenesis . . .	352
3.1.	Stochastic Equations of State Variables . . . . .	353
3.2.	The Expected Number of $I_j(t)$ . . . . .	354
3.3.	The Probability Distribution of the Number of Detectable Tumors . . . . .	355
4.	A Statistical Model and the Probability Distribution of Cancer Incidence Data . . . . .	356
4.1.	Data Augmentation and the Expanded Model . . .	358
4.2.	The Genetic Parameters . . . . .	359
5.	The State Space Model and the Generalized Bayesian Approach for Estimating the Unknown Parameters . . . .	361
5.1.	The Prior Distribution of the Parameters . . . . .	361
5.2.	The Posterior Distribution of the Parameters Given $\{Y, Z\}$ . . . . .	362
5.3.	The Multi-Level Gibbs Sampling Procedure for Estimating Parameters . . . . .	363
5.4.	The Genetic Algorithm . . . . .	364
6.	Application and Results . . . . .	364
7.	Conclusions and Discussion . . . . .	370
	Acknowledgments . . . . .	371
	References . . . . .	371
12.	Cancer Risk Assessment of Environmental Agents by Stochastic and State Space Models of Carcinogenesis . . . . .	375
	<i>Wai Y. Tan, Chao W. Chen and Li J. Zhang</i>	
1.	Introduction . . . . .	375
2.	A General Stochastic Model of Carcinogenesis . . . . .	377
2.1.	The Stochastic Difference Equations for State Variables . . . . .	380
2.2.	The Probability of Developing Cancer Tumors . . .	381
2.3.	Probability Distribution of the State Variables . . .	381
3.	The Data for Risk Assessment of Environmental Agents . .	382

4.	State Space Models of Carcinogenesis and the Prediction of State Variables . . . . .	383
5.	A State Space Model for Cancer Risk Assessment . . . . .	384
5.1.	The Stochastic System Model and Probability Distributions . . . . .	384
5.2.	The Observation Model . . . . .	385
6.	The Genetic Algorithm and the Predicted Inference Procedures . . . . .	386
6.1.	The Genetic Algorithm . . . . .	386
6.2.	The Predictive Inference Procedures . . . . .	387
7.	Developing Confidence Intervals for Probabilities of Developing Cancer by Genetic Algorithm . . . . .	388
8.	Developing Dose-Response Curves of Environmental Agents by Genetic Algorithm . . . . .	388
9.	An Application and Illustration . . . . .	389
10.	Conclusions . . . . .	394
	Acknowledgments . . . . .	394
	References . . . . .	394
13.	Stochastic Models for Preneoplastic Lesions and Their Application for Cancer Risk Assessment . . . . .	397
	<i>Annette Kopp-Schneider, Iris Burkholder, Jutta Groos and Lutz Edler</i>	
1.	Introduction . . . . .	397
2.	Modeling Preneoplastic Lesions . . . . .	401
2.1.	The Multistage Model with Clonal Expansion of Intermediate Cells . . . . .	401
2.2.	A Geometric Model for Colonies of Intermediate Cells . . . . .	405
2.3.	Comparison of Multistage and Color-Shift Model . . . . .	406
3.	Application of Carcinogenesis Models to Preneoplastic Lesion Data . . . . .	408
3.1.	Mouse Skin Carcinogenesis: Testing Biological Hypotheses about Papilloma and Carcinoma Formation . . . . .	408

3.2.	Liver Focal Lesion Data: Testing Hypotheses about FAH Formation and Phenotype Change . . . . .	411
3.3.	Liver Focal Lesion Data: Dose-Response Analyses . . . . .	412
4.	Discussion . . . . .	416
	Acknowledgments . . . . .	418
	References . . . . .	418
	Appendix A: Basic Ideas of the Color-Shift Model . . . . .	422
	Appendix B: Likelihood Functions . . . . .	423
	Appendix B(1): Likelihood Function for Skin Papilloma and Carcinoma Data . . . . .	423
	Appendix B(2): Likelihood Function for Liver Focal Lesion Data . . . . .	424
14.	Drug Resistance in Cancer Models . . . . .	425
	<i>Jaroslav Smieja</i>	
1.	Introduction . . . . .	425
2.	Biological Background . . . . .	426
3.	Preliminaries for Mathematical Models . . . . .	429
4.	Drug Resistance and a Single Chemotherapeutic Agent . . . . .	431
4.1.	A Simple, Two-Compartmental Model . . . . .	431
4.2.	Evolution of Drug Resistance Stemming from Gene Amplification . . . . .	434
4.3.	Partial Sensitivity of the Resistant Subpopulation . . . . .	439
4.4.	Phase-Specific Chemotherapy . . . . .	440
4.5.	General Compartmental Model . . . . .	442
5.	Multidrug Therapy and Drug Resistance . . . . .	447
5.1.	A Two-Compartmental Model . . . . .	448
5.2.	A Four-Compartmental Model . . . . .	448
6.	Concluding Remarks . . . . .	449
	Acknowledgments . . . . .	451
	References . . . . .	452
15.	Bladder Cancer Screening by Magnetic Resonance Imaging . . . . .	457
	<i>Lihong Li, Zigang Wang and Zhengrong Liang</i>	
1.	Introduction . . . . .	458

2.	Methods . . . . .	459
2.1.	MR Image Protocols . . . . .	459
2.2.	Image Segmentation . . . . .	461
2.3.	Interactive Visualization System . . . . .	462
2.4.	Detection of Bladder Lesions . . . . .	463
3.	Results . . . . .	465
4.	Discussion and Conclusions . . . . .	466
	Acknowledgments . . . . .	467
	References . . . . .	468
16.	Mathematical Framework and Wavelets Applications in Proteomics for Cancer Study . . . . .	471
	<i>Don Hong and Yu Shyr</i>	
1.	Introduction . . . . .	471
2.	Mathematical Representation and Preprocessing of Maldi MS Data . . . . .	475
2.1.	Mathematical Model for MALDI-TOF MS Data . . . . .	476
2.1.1.	Baseline correction and normalization . . . . .	479
2.1.2.	Spectra registration and peak alignment . . . . .	480
3.	Multiscale Tools . . . . .	482
3.1.	Wavelets and WaveSpec Software . . . . .	483
3.2.	Diffusion Maps . . . . .	488
4.	Clustering and Cancer Data Classifications . . . . .	489
	Acknowledgments . . . . .	496
	References . . . . .	496
17.	Advanced Statistical Methods for the Design and Analysis of Tumor Xenograft Experiments . . . . .	501
	<i>Ming Tan and Hong-Bin Fang</i>	
1.	Introduction . . . . .	502
2.	Design of Experiments for Combination Studies . . . . .	504
2.1.	Fixed-Ratio Design and Ray Design . . . . .	506
2.2.	Abdelbasit-Plackett Optimal Experimental Design . . . . .	506
2.3.	Uniform Experimental Design . . . . .	507
3.	Statistical Analysis for Tumor Growth . . . . .	509

3.1.	Statistical Models . . . . .	510
3.2.	Parameter Estimation via the ECM Algorithm . . . . .	512
4.	Comparison of Treatment Effects . . . . .	514
4.1.	Quasi $t$ -Test Based on the EM Algorithm . . . . .	515
4.2.	Bayesian Test . . . . .	516
5.	Summary and Discussion . . . . .	516
	Acknowledgments . . . . .	518
	References . . . . .	518
18.	Analysis of Occult Tumor Studies . . . . .	521
	<i>Shesh N. Rai</i>	
1.	Introduction . . . . .	521
2.	A Review of the Literature . . . . .	523
3.	Preliminary Considerations . . . . .	527
3.1.	Constructing the Likelihood Function . . . . .	530
3.2.	Non-Parametric Settings . . . . .	531
3.3.	Fitting the Semi-Parametric Model . . . . .	534
4.	Interval Estimation . . . . .	539
5.	Testing Tumor Lethality and Carcinogenic Effect . . . . .	543
6.	Two Examples . . . . .	546
7.	Discussion . . . . .	556
	References . . . . .	560
	Index . . . . .	563