

Contents

Preface	vii
Glossary	xi
1 Introduction	1
1.1 The Scope of Recurrent Events	1
1.2 Some Preliminary Examples	2
1.2.1 Mammary Tumors in a Carcinogenicity Study.....	2
1.2.2 Testing and Debugging a Large Software System	5
1.2.3 Pulmonary Exacerbations in Cystic Fibrosis	5
1.2.4 Automobile Warranty Claims	7
1.3 Notation and Frameworks	9
1.3.1 Methods Based on Event Counts	11
1.3.2 Methods Based on Waiting or Gap Times	12
1.3.3 More General Models	14
1.3.4 Covariates	14
1.3.5 Factors Influencing Model Choice.....	15
1.4 Selection of Individuals and Observation Schemes.....	16
1.4.1 The Choice of Time Scale	16
1.4.2 Defining Periods “At Risk”	18
1.4.3 Initial Conditions and Selecting Individuals for Study ..	19
1.4.4 Intermittent Observation and Interval Censoring	20
1.5 Multitype Event Data.....	20
1.5.1 Multivariate Event Processes	20
1.5.2 Recurrent Events with Termination	20
1.5.3 Recurrent Episodes	21
1.6 Some Other Aspects of Analysis and Design	23
1.7 Bibliographic Notes	24

2	Models and Frameworks for Analysis of Recurrent Events	27
2.1	Mathematical Background	27
2.2	Poisson Processes and Models for Event Counts	31
2.2.1	Poisson Processes	31
2.2.2	Covariates in Poisson Processes	34
2.2.3	Random Effects in Poisson Processes	35
2.2.4	Example: Mammary Tumors in Rats	37
2.3	Renewal Processes and Models for Gap Times	39
2.3.1	Models for Gap Times Between Events	39
2.3.2	Example: Bowel Motility Cycles	42
2.4	General Intensity-Based Models	43
2.5	Discrete-Time Models and Time-Varying Covariates	45
2.6	Likelihood for Selection and Observation Schemes	47
2.7	Bibliographic Notes	51
2.8	Problems and Supplements	52
3	Methods Based on Counts and Rate Functions	59
3.1	Introduction	59
3.2	Parametric Maximum Likelihood for Poisson Models	61
3.2.1	Score and Information Functions	61
3.2.2	A General Parametric Rate Function	62
3.2.3	Time Transform Models	63
3.2.4	Using Survival Software	64
3.3	Poisson Models with Piecewise-Constant Rates	65
3.4	Nonparametric and Semiparametric Poisson Models	68
3.4.1	Nonparametric Inference	68
3.4.2	Semiparametric Regression	70
3.4.3	Stratification	73
3.4.4	Additive Models	75
3.5	Poisson Models with Random Effects	76
3.5.1	Formulation	76
3.5.2	Models for Zero-Inflated Data	78
3.5.3	Negative Binomial Models	79
3.6	Robust Methods for Rate and Mean Functions	82
3.6.1	Nonparametric Estimation	82
3.6.2	Parametric Estimation	83
3.6.3	Robust Semiparametric Methods	84
3.6.4	Robust Methods with Semiparametric Variances	86
3.6.5	Methods Based on Multivariate Failure Time Data	86
3.7	Some Useful Tests for Rate Functions	88
3.7.1	Tests for Trend	88
3.7.2	Tests for Multiplicative Covariate Effects	90
3.7.3	Generalized Residuals, Martingales, and Assessment of Fit	92

3.7.4	Tests for Extra-Poisson Variation	97
3.7.5	Two-Sample Test Statistics Based on Rates	97
3.8	Applications and Illustrations	100
3.8.1	Rat Mammary Tumor Data	100
3.8.2	A Trial of Treatment for Herpes Simplex Virus	105
3.8.3	Fitting and Prediction from a Software Debugging Model	107
3.8.4	Comparing Warranty Claim Histories	110
3.9	Bibliographic Notes	112
3.10	Problems and Supplements	114
4	Analysis of Gap Times	121
4.1	Renewal Processes and Related Methods of Analysis	121
4.2	Extensions of Renewal Models	126
4.2.1	Conditional Analysis of Successive Gap Times	126
4.2.2	Models with Random Effects	128
4.2.3	Joint Gap Time Distributions	129
4.2.4	Modulated Renewal Processes	132
4.3	Examples	133
4.3.1	Bowel Motility Cycles	133
4.3.2	Pulmonary Exacerbations and rhDNase Treatment	134
4.4	Estimation of Marginal Gap Time Probabilities	137
4.4.1	Nonparametric Estimation of Marginal Gap Time Distributions	139
4.4.2	Estimation for Marginal Regression Models	143
4.4.3	Pulmonary Exacerbations in Cystic Fibrosis	143
4.5	Left Truncation of First Gap Times and Initial Conditions	146
4.5.1	Initial Conditions and Renewal Processes	147
4.5.2	Initial Conditions and General Gap Time Analysis	150
4.6	Bibliographic Notes	152
4.7	Problems and Supplements	153
5	General Intensity-Based Models	161
5.1	Time Scales and Intensity Modeling	161
5.2	Parametric Analysis for Two Useful Models	163
5.2.1	Log-Linear Intensity Models	163
5.2.2	A Trend-Renewal Model	165
5.2.3	Model Checking	167
5.2.4	An Illustration: Air-Conditioning System Failures	167
5.3	Semiparametric Markov Analysis	171
5.3.1	Models with Dependence on Prior Counts	171
5.3.2	Markov Nonparametric Estimation	173
5.3.3	Models with Covariates	175
5.3.4	Analysis of Outbreaks Due to Herpes Simplex Virus	177

5.4	Semiparametric Modulated Renewal Analysis	183
5.4.1	Analysis Based on the Cox Model	183
5.4.2	Illustration: Cerebrospinal Fluid Shunts	185
5.5	Some Additional Illustrations	189
5.5.1	Pulmonary Exacerbations in the Study of rhDNase	190
5.5.2	Analysis of Asthma Exacerbations	193
5.6	Bibliographic Notes	200
5.7	Problems and Supplements	201
6	Multitype Recurrent Events	205
6.1	Multivariate Event Data	205
6.2	Intensity-Based Methods	206
6.2.1	Notation and Intensity Functions	206
6.2.2	Remarks on Intensity-Based Models	207
6.3	Random Effect Models for Multitype Events	209
6.4	Robust Methods for Multitype Events	212
6.4.1	Methods Based on Working Independence Assumptions	212
6.4.2	Robust Methods with Covariance Functions	214
6.5	Alternating Two-State Processes	216
6.6	Recurrent Events with a Terminal Event	218
6.6.1	Intensity-Based Approaches	219
6.6.2	Random Effects Models	220
6.6.3	Robust Methods for Marginal Features	222
6.6.4	Partially Conditional Methods	224
6.7	Applications and Illustrations	227
6.7.1	Cerebrospinal Fluid Shunt Failures	227
6.7.2	Exacerbations in Patients with Chronic Bronchitis	232
6.7.3	Skeletal Complications in Metastatic Cancer	236
6.7.4	Relationships Between Skeletal Complications	241
6.8	Bibliographic Notes	246
6.9	Problems and Supplements	247
7	Observation Schemes Giving Incomplete or Selective Data .	251
7.1	Intermittent Observation During Followup	251
7.1.1	Methods Based on Poisson Processes	252
7.1.2	Robust Estimation of Rate and Mean Functions	254
7.1.3	Illustration: Superficial Tumors of the Bladder	256
7.1.4	Interval-Count Data for Multiple Events	260
7.1.5	Illustration: Joint Damage in Psoriatic Arthritis	263
7.2	Dependent Censoring or Inspections	264
7.2.1	Dependent Censoring and Weighted Estimating Functions	264
7.2.2	Rate or Mean Function Estimation with Event- Dependent Censoring	268
7.2.3	Intermittent Observation	270

7.3	Event-Dependent Selection	273
7.3.1	Some Examples	273
7.3.2	Supplementary Information on Selection.....	281
7.4	Bibliographic Notes	284
7.5	Problems and Supplements	286
8	Other Topics	293
8.1	Event Processes with Marks	293
8.2	Models for Cumulative Costs.....	295
8.2.1	Introduction	295
8.2.2	Estimation for Cost Processes.....	297
8.2.3	Examples	299
8.3	Prediction	302
8.3.1	Introduction	302
8.3.2	Predictive Probabilities and Calibration	304
8.3.3	Some Examples of Prediction	306
8.4	Recurrent Events in Randomized Trials	311
8.4.1	Specification and Testing of Treatment Effects	311
8.4.2	Trial Design for Mixed Poisson Processes	315
8.4.3	Use of Baseline Count Data.....	316
8.4.4	Interim Monitoring with Recurrent Events.....	320
8.5	Clustered Data.....	324
8.6	Missing Covariate Values	327
8.7	Covariate Measurement Error	329
8.8	Bayesian Methods	331
8.9	Bibliographic Notes.....	332
8.10	Problems and Supplements	333
A	Estimation and Statistical Inference	337
A.1	Maximum Likelihood	337
A.1.1	Introduction	337
A.1.2	Asymptotic Pivotal	338
A.1.3	Confidence Regions or Intervals	340
A.1.4	Tests of Hypotheses	341
A.2	Estimating Functions	342
B	Computational Methods	345
B.1	Software for Recurrent Events.....	345
B.2	Optimization Methods	346
B.3	Simulation and Resampling Methods.....	346
C	Code and Remarks for Selected Examples	349
C.1	Tumorigenicity Data Analysis of Chapter 3.....	349
C.1.1	Poisson Analysis with Weibull Baseline Rate.....	349
C.1.2	Poisson Analysis with Piecewise-Constant Rates.....	351

C.1.3	Nonparametric and Semiparametric Poisson Analysis ..	353
C.1.4	Semiparametric Mixed Poisson Analysis	353
C.1.5	Robust Semiparametric Analysis	354
C.2	Code for rhDNase Data Analyses of Chapter 4	355
C.3	Code for Chronic Bronchitis Trial of Chapter 6	358
D	Datasets	363
D.1	Bladder Cancer Data	363
D.2	Bowel Motility Data	364
D.3	Pulmonary Exacerbations and rhDNase	365
D.4	Software Debugging Data.....	367
D.5	Artificial Field Repair Data	367
	References	371
	Author Index	391
	Subject Index	397