

Contents

Preface	xv
1 Survival analysis	1
1.1 Special features of survival data	1
1.1.1 Censoring	2
1.1.2 Independent censoring	3
1.1.3 Study time and patient time	3
1.2 Some examples	5
1.3 Survivor, hazard and cumulative hazard functions	10
1.3.1 The survivor function	10
1.3.2 The hazard function	12
1.3.3 The cumulative hazard function	13
1.4 Computer software for survival analysis	14
1.5 Further reading	15
2 Some non-parametric procedures	17
2.1 Estimating the survivor function	17
2.1.1 Life-table estimate of the survivor function	19
2.1.2 Kaplan-Meier estimate of the survivor function	21
2.1.3 Nelson-Aalen estimate of the survivor function	24
2.2 Standard error of the estimated survivor function	25
2.2.1 Standard error of the Kaplan-Meier estimate	26
2.2.2 Standard error of other estimates	27
2.2.3 Confidence intervals for values of the survivor function	28
2.3 Estimating the hazard function	31
2.3.1 Life-table estimate of the hazard function	31
2.3.2 Kaplan-Meier type estimate	32
2.3.3 Estimating the cumulative hazard function	35
2.4 Estimating the median and percentiles of survival times	36
2.5 Confidence intervals for the median and percentiles	38
2.6 Comparison of two groups of survival data	40
2.6.1 Hypothesis testing	41
2.6.2 The log-rank test	44
2.6.3 The Wilcoxon test	48
2.6.4 Comparison of the log-rank and Wilcoxon tests	49

2.7	Comparison of three or more groups of survival data	50
2.8	Stratified tests	52
2.9	Log-rank test for trend	54
2.10	Further reading	56
3	The Cox regression model	57
3.1	Modelling the hazard function	57
3.1.1	A model for the comparison of two groups	58
3.1.2	The general proportional hazards model	59
3.2	The linear component of the model	60
3.2.1	Including a variate	61
3.2.2	Including a factor	61
3.2.3	Including an interaction	62
3.2.4	Including a mixed term	63
3.3	Fitting the Cox regression model	65
3.3.1	Likelihood function for the model	67
3.3.2	Treatment of ties	69
3.3.3	The Newton-Raphson procedure	71
3.4	Confidence intervals and hypothesis tests	72
3.4.1	Confidence intervals for hazard ratios	73
3.4.2	Two examples	73
3.5	Comparing alternative models	76
3.5.1	The statistic $-2 \log \hat{L}$	77
3.5.2	Comparing nested models	78
3.6	Strategy for model selection	83
3.6.1	Variable selection procedures	84
3.7	Variable selection using the lasso	90
3.7.1	The lasso in Cox regression modelling	91
3.7.2	Data preparation	92
3.8	Non-linear terms	95
3.8.1	Testing for non-linearity	96
3.8.2	Modelling non-linearity	97
3.8.3	Fractional polynomials	98
3.9	Interpretation of parameter estimates	99
3.9.1	Models with a variate	99
3.9.2	Models with a factor	100
3.9.3	Models with combinations of terms	104
3.10	Estimating the hazard and survivor functions	107
3.10.1	The special case of no covariates	110
3.10.2	Some approximations to estimates of baseline functions	110
3.11	Risk adjusted survivor function	116
3.11.1	Risk adjusted survivor function for groups of individuals	117
3.12	Explained variation in the Cox regression model	120
3.12.1	Measures of explained variation	122
3.12.2	Measures of predictive ability	123

3.12.3	Model validation	124
3.13	Proportional hazards and the log-rank test	125
3.14	Further reading	128
4	Model checking in the Cox regression model	131
4.1	Residuals for the Cox regression model	131
4.1.1	Cox-Snell residuals	132
4.1.2	Modified Cox-Snell residuals	133
4.1.3	Martingale residuals	135
4.1.4	Deviance residuals	136
4.1.5	Schoenfeld residuals	137
4.1.6	Score residuals	138
4.2	Assessment of model fit	142
4.2.1	Plots based on the Cox-Snell residuals	142
4.2.2	Plots based on the martingale and deviance residuals	145
4.2.3	Checking the functional form of covariates	147
4.3	Identification of influential observations	152
4.3.1	Influence of observations on a parameter estimate	153
4.3.2	Influence of observations on the set of parameter estimates	155
4.3.3	Treatment of influential observations	158
4.4	Testing the assumption of proportional hazards	160
4.4.1	The log-cumulative hazard plot	161
4.4.2	Use of Schoenfeld residuals	163
4.4.3	Tests for non-proportional hazards	164
4.4.4	Adding a time-dependent variable	166
4.5	Recommendations	168
4.6	Further reading	169
5	Parametric proportional hazards models	171
5.1	Models for the hazard function	171
5.1.1	The exponential distribution	172
5.1.2	The Weibull distribution	173
5.2	Assessing the suitability of a parametric model	177
5.3	Fitting a parametric model to a single sample	178
5.3.1	Likelihood function for randomly censored data	180
5.4	Fitting exponential and Weibull models	181
5.4.1	Fitting the exponential distribution	182
5.4.2	Fitting the Weibull distribution	186
5.4.3	Standard error of a percentile of the Weibull distribution	188
5.5	A model for the comparison of two groups	192
5.5.1	The log-cumulative hazard plot	192
5.5.2	Fitting the model	194
5.6	The Weibull proportional hazards model	199
5.6.1	Fitting the model	200

5.6.2	Standard error of a percentile in the Weibull model	201
5.6.3	Log-linear form of the model	203
5.6.4	Exploratory analyses	205
5.7	Comparing alternative Weibull models	208
5.8	Explained variation in the Weibull model	215
5.9	The Gompertz proportional hazards model	216
5.10	Model choice	218
5.11	Further reading	219
6	Accelerated failure time and other parametric models	221
6.1	Probability distributions for survival data	221
6.1.1	The log-logistic distribution	222
6.1.2	The lognormal distribution	222
6.1.3	The gamma distribution	224
6.1.4	The inverse Gaussian distribution	225
6.2	Exploratory analyses	225
6.3	Accelerated failure model for two groups	227
6.3.1	Comparison with the proportional hazards model	228
6.3.2	The percentile-percentile plot	231
6.4	The general accelerated failure time model	232
6.4.1	Log-linear form of the accelerated failure time model	234
6.5	Parametric accelerated failure time models	236
6.5.1	The Weibull accelerated failure time model	236
6.5.2	The log-logistic accelerated failure time model	239
6.5.3	The lognormal accelerated failure time model	240
6.5.4	Summary	241
6.6	Fitting and comparing accelerated failure time models	243
6.7	The proportional odds model	250
6.7.1	The log-logistic proportional odds model	253
6.8	Some other distributions for survival data	255
6.9	Flexible parametric models	256
6.9.1	The Royston and Parmar model	259
6.9.2	Number and position of the knots	262
6.9.3	Fitting the model	262
6.9.4	Proportional odds models	266
6.10	Modelling cure rates	268
6.11	Effect of covariate adjustment	270
6.12	Further reading	272
7	Model checking in parametric models	275
7.1	Residuals for parametric models	275
7.1.1	Standardised residuals	275
7.1.2	Cox-Snell residuals	276
7.1.3	Martingale residuals	277
7.1.4	Deviance residuals	277

7.1.5	Score residuals	277
7.2	Residuals for particular parametric models	278
7.2.1	Weibull distribution	279
7.2.2	Log-logistic distribution	279
7.2.3	Lognormal distribution	280
7.2.4	Analysis of residuals	280
7.3	Comparing observed and fitted survivor functions	284
7.4	Identification of influential observations	287
7.4.1	Influence of observations on a parameter estimate	287
7.4.2	Influence of observations on the set of parameter estimates	288
7.5	Testing proportional hazards in the Weibull model	291
7.6	Further reading	292
8	Time-dependent variables	295
8.1	Types of time-dependent variables	295
8.2	A model with time-dependent variables	296
8.2.1	Fitting the Cox model	297
8.2.2	Estimation of baseline hazard and survivor functions	300
8.3	Model comparison and validation	302
8.3.1	Comparison of treatments	303
8.3.2	Assessing model adequacy	303
8.4	Some applications of time-dependent variables	304
8.5	Three examples	306
8.6	Counting process format	316
8.7	Further reading	317
9	Interval-censored survival data	319
9.1	Modelling interval-censored survival data	319
9.2	Modelling the recurrence probability in the follow-up period	322
9.3	Modelling the recurrence probability at different times	325
9.4	Arbitrarily interval-censored survival data	332
9.4.1	Modelling arbitrarily interval-censored data	332
9.4.2	Proportional hazards model for the survivor function	334
9.4.3	Choice of the step times	337
9.5	Parametric models for interval-censored data	342
9.6	Discussion	343
9.7	Further reading	344
10	Frailty models	345
10.1	Introduction to frailty	345
10.1.1	Random effects	346
10.1.2	Individual frailty	346
10.1.3	Shared frailty	347
10.2	Modelling individual frailty	348

10.2.1	Frailty distributions	349
10.2.2	Observable survivor and hazard functions	351
10.3	The gamma frailty distribution	352
10.3.1	Impact of frailty on an observable hazard function	353
10.3.2	Impact of frailty on an observable hazard ratio	354
10.4	Fitting parametric frailty models	356
10.4.1	Gamma frailty	357
10.5	Fitting semi-parametric frailty models	363
10.5.1	Lognormal frailty effects	363
10.5.2	Gamma frailty effects	365
10.6	Comparing models with frailty	366
10.6.1	Testing for the presence of frailty	366
10.7	The shared frailty model	372
10.7.1	Fitting the shared frailty model	373
10.7.2	Comparing shared frailty models	374
10.8	Some other aspects of frailty modelling	377
10.8.1	Model checking	377
10.8.2	Correlated frailty models	378
10.8.3	Dependence measures	378
10.8.4	Numerical problems in model fitting	378
10.9	Further reading	379
11	Non-proportional hazards and institutional comparisons	381
11.1	Non-proportional hazards	381
11.2	Stratified proportional hazards models	383
11.2.1	Non-proportional hazards between treatments	385
11.3	Restricted mean survival	389
11.3.1	Use of pseudo-values	391
11.4	Institutional comparisons	393
11.4.1	Interval estimate for the <i>RAFR</i>	397
11.4.2	Use of the Poisson regression model	400
11.4.3	Random institution effects	402
11.5	Further reading	403
12	Competing risks	405
12.1	Introduction to competing risks	405
12.2	Summarising competing risks data	406
12.2.1	Kaplan-Meier estimate of survivor function	407
12.3	Hazard and cumulative incidence functions	409
12.3.1	Cause-specific hazard function	409
12.3.2	Cause-specific cumulative incidence function	410
12.3.3	Some other functions of interest	413
12.4	Modelling cause-specific hazards	414
12.4.1	Likelihood functions for competing risks models	415
12.4.2	Parametric models for cumulative incidence functions	418

CONTENTS

xiii

12.5	Modelling cause-specific incidence	419
12.5.1	The Fine and Gray competing risks model	419
12.6	Model checking	422
12.7	Further reading	428
13	Multiple events and event history modelling	429
13.1	Introduction to counting processes	429
13.1.1	Modelling the intensity function	430
13.1.2	Survival data as a counting process	431
13.1.3	Survival data in the counting process format	433
13.1.4	Robust estimation of the variance-covariance matrix	434
13.2	Modelling recurrent event data	435
13.2.1	The Anderson and Gill model	436
13.2.2	The Prentice, Williams and Peterson model	437
13.3	Multiple events	443
13.3.1	The Wei, Lin and Weissfeld model	443
13.4	Event history analysis	448
13.4.1	Models for event history analysis	449
13.5	Further reading	455
14	Dependent censoring	457
14.1	Identifying dependent censoring	457
14.2	Sensitivity to dependent censoring	458
14.2.1	A sensitivity analysis	459
14.2.2	Impact of dependent censoring	461
14.3	Modelling with dependent censoring	463
14.3.1	Cox regression model with dependent censoring	464
14.4	Further reading	470
15	Sample size requirements for a survival study	471
15.1	Distinguishing between two treatment groups	471
15.2	Calculating the required number of deaths	472
15.2.1	Derivation of the required number of deaths	474
15.3	Calculating the required number of patients	479
15.3.1	Derivation of the required number of patients	480
15.3.2	An approximate procedure	483
15.4	Further reading	484
A	Maximum likelihood estimation	487
A.1	Inference about a single unknown parameter	487
A.2	Inference about a vector of unknown parameters	489

B Additional data sets	491
B.1 Chronic active hepatitis	491
B.2 Recurrence of bladder cancer	492
B.3 Survival of black ducks	492
B.4 Bone marrow transplantation	495
B.5 Chronic granulomatous disease	495

Bibliography	499
---------------------	------------

Index of Examples	521
--------------------------	------------

Index	523
--------------	------------