
Contents

Preface	iii
1 Introduction	1
1.1 Goals	1
1.2 Motivating Studies	2
1.2.1 Primary Biliary Cirrhosis Data	2
1.2.2 AIDS Data	3
1.2.3 Liver Cirrhosis Data	4
1.2.4 Aortic Valve Data	6
1.2.5 Other Applications	7
1.3 Inferential Objectives in Longitudinal Studies	8
1.3.1 Effect of Covariates on a Single Outcome	9
1.3.2 Association Between Outcomes	9
1.3.3 Complex Hypothesis Testing	10
1.3.4 Prediction	10
1.3.5 Statistical Analysis with Implicit Outcomes	11
1.4 Overview	11
2 Longitudinal Data Analysis	15
2.1 Features of Longitudinal Data	15
2.2 Linear Mixed-Effects Models	16
2.2.1 Estimation	18
2.2.2 Implementation in R	21
2.3 Missing Data in Longitudinal Studies	27
2.3.1 Missing Data Mechanisms	29
2.3.2 Missing Not At Random Model Families	32
2.4 Further Reading	34
3 Analysis of Event Time Data	35
3.1 Features of Event Time Data	35
3.2 Basic Functions in Survival Analysis	37
3.2.1 Likelihood Construction for Censored Data	40
3.3 Relative Risk Regression Models	41
3.3.1 Implementation in R	42
3.4 Time-Dependent Covariates	44
3.5 Extended Cox Model	46

3.6	Further Reading	49
4	Joint Models for Longitudinal and Time-to-Event Data	51
4.1	The Basic Joint Model	51
4.1.1	The Survival Submodel	52
4.1.2	The Longitudinal Submodel	54
4.2	Joint Modeling in R: A Comparison with the Extended Cox Model	56
4.3	Estimation of Joint Models	61
4.3.1	Two-Stage Approaches	61
4.3.2	Joint Likelihood Formulation	62
4.3.3	Standard Errors with an Unspecified Baseline Risk Function	66
4.3.4	Optimization Control in JM	67
4.3.5	Numerical Integration	68
4.3.6	Numerical Integration Control in JM	72
4.3.7	Convergence Problems	74
4.4	Asymptotic Inference for Joint Models	78
4.4.1	Hypothesis Testing	78
4.4.2	Confidence Intervals	84
4.4.3	Design Considerations	86
4.5	Estimation of the Random Effects	87
4.6	Connection with the Missing Data Framework	89
4.7	Sensitivity Analysis under Joint Models	92
5	Extensions of the Standard Joint Model	97
5.1	Parameterizations	97
5.1.1	Interaction Effects	98
5.1.2	Lagged Effects	100
5.1.3	Time-Dependent Slopes Parameterization	103
5.1.4	Cumulative Effects Parameterization	106
5.1.5	Random-Effects Parameterization	111
5.2	Handling Exogenous Time-Dependent Covariates	115
5.3	Stratified Relative Risk Models	119
5.4	Latent Class Joint Models	122
5.5	Multiple Failure Times	128
5.5.1	Competing Risks	128
5.5.2	Recurrent Events	134
5.6	Accelerated Failure Time Models	137
5.7	Joint Models for Categorical Longitudinal Outcomes	139
5.7.1	The Generalized Linear Mixed Model (GLMM)	139
5.7.2	Combining Discrete Repeated Measures with Survival	141
5.8	Joint Models for Multiple Longitudinal Outcomes	142

6	Joint Model Diagnostics	145
6.1	Residuals for Joint Models	145
6.1.1	Residuals for the Longitudinal Part	145
6.1.2	Residuals for the Survival Part	148
6.2	Dropout and Residuals	155
6.3	Multiple Imputation Residuals	158
6.3.1	Fixed Visit Times	158
6.3.2	Random Visit Times	162
6.4	Random-Effects Distribution	169
7	Prediction and Accuracy in Joint Models	171
7.1	Dynamic Predictions of Survival Probabilities	171
7.1.1	Definition	171
7.1.2	Estimation	172
7.1.3	Implementation in R	174
7.2	Dynamic Predictions for the Longitudinal Outcome	182
7.3	Effect of Parameterization on Predictions	186
7.4	Prospective Accuracy for Joint Models	194
7.4.1	Discrimination Measures for Binary Outcomes	195
7.4.2	Discrimination Measures for Survival Outcomes	197
7.4.3	Prediction Rules for Longitudinal Markers	198
7.4.4	Discrimination Indices	200
7.4.5	Estimation under the Joint Modeling Framework	202
7.4.6	Implementation in R	205
A	A Brief Introduction to R	219
A.1	Obtaining and Installing R and R Packages	219
A.2	Simple Manipulations	220
A.2.1	Basic R Objects	220
A.2.2	Indexing	222
A.3	Import and Manipulate Data Frames	224
A.4	The Formula Interface	226
B	The EM Algorithm for Joint Models	229
B.1	A Short Description of the EM Algorithm	229
B.2	The E-step for Joint Models	230
B.3	The M-step for Joint Models	231
C	Structure of the JM Package	235
C.1	Methods for Standard Generic Functions	235
C.2	Additional Functions	237
	References	239
	Index	257