CONTENTS

LIST OF CONTRIBUTORS xvii
PREFACE xxi

PART I ADVANCES IN BIOMEDICAL AND HEALTH INFORMATICS 1

1 Recent Development in Methodology for Gene Network Problems and Inferences 3
Sung W. Han and Hua Zhong

1.1 Introduction 3
1.2 Background 5
1.3 Genetic Data Available 7
1.4 Methodology 7
  1.4.1 Structural Equation Model 8
  1.4.2 Score Function Formulation 9
  1.4.3 Two-Stage Learning 12
  1.4.4 Further Issues 13
1.5 Search Algorithm 13
  1.5.1 Global Optimal Solution Search 13
  1.5.2 Heuristic Algorithm for a Local Optimal Solution 14
1.6 PC Algorithm 15
2 Biomedical Analytics and Morphoproteomics: An Integrative Approach for Medical Decision Making for Recurrent or Refractory Cancers

Mary F. McGuire and Robert E. Brown

2.1 Introduction 31
2.2 Background 32
2.2.1 Data 33
2.2.2 Tools 33
2.2.3 Algorithms 34
2.2.4 Literature Review 35
2.3 Methodology 37
2.3.1 Morphoproteomics (Fig. 2.1(1–3)) 39
2.3.2 Biomedical Analytics (Fig. 2.1(4–10)) 40
2.3.3 Integrating Morphoproteomics and Biomedical Analytics 44
2.4 Case Studies 46
2.4.1 Clinical: Therapeutic Recommendations for Pancreatic Adenocarcinoma 46
2.4.2 Clinical: Biology Underlying Exceptional Responder in Refractory Hodgkin’s Lymphoma 48
2.4.3 Research: Role of the Hypoxia Pathway in Both Oncogenesis and Embryogenesis 50
2.5 Discussion 51
2.6 Conclusions 52
Acknowledgments 53
References 53

3 Characterization and Monitoring of Nonlinear Dynamics and Chaos in Complex Physiological Systems

Hui Yang, Yun Chen, and Fabio Leonelli

3.1 Introduction 59
3.2 Background 61
3.3 Sensor-Based Characterization and Modeling of Nonlinear Dynamics 65
4 Statistical Modeling of Electrocardiography Signal for Subject Monitoring and Diagnosis 95

Lili Chen, Changyue Song, and Xi Zhang

4.1 Introduction 95
4.2 Basic Elements of ECG 96
4.3 Statistical Modeling of ECG for Disease Diagnosis 99
  4.3.1 ECG Signal Denoising 100
  4.3.2 Waveform Detection 105
  4.3.3 Feature Extraction 106
  4.3.4 Disease Classification and Diagnosis 111
4.4 An Example: Detection of Obstructive Sleep Apnea from a Single ECG Lead 115
  4.4.1 Introduction to Obstructive Sleep Apnea 115
4.5 Materials and Methods 115
  4.5.1 Database 115
  4.5.2 QRS Detection and RR Correction 116
  4.5.3 R Wave Amplitudes and EDR Signal 117
  4.5.4 Feature Set 117
  4.5.5 Classifier Training with Feature Selection 118
4.6 Results 118
  4.6.1 QRS Detection and RR Correction 118
  4.6.2 Feature Selection 118
  4.6.3 OSA Detection 120
4.7 Conclusions and Discussions 121
References 121

5 Modeling and Simulation of Measurement Uncertainty in Clinical Laboratories 127

Varun Ramamohan, James T. Abbott, and Yuehwern Yih

5.1 Introduction 127
5.2 Background and Literature Review 129
### 5.2 Measurement Uncertainty: Background and Analytical Estimation

- 5.2.1 Measurement Uncertainty: Background and Analytical Estimation 130
- 5.2.2 Uncertainty in Clinical Laboratories 134
- 5.2.3 Uncertainty in Clinical Laboratories: A System Approach 136

### 5.3 Model Development Guidelines

- 5.3.1 System Description and Process Phases 138
- 5.3.2 Modeling Guidelines 139

### 5.4 Implementation of Guidelines: Enzyme Assay Uncertainty Model

- 5.4.1 Calibration Phase 141
- 5.4.2 Sample Analysis Phase 149
- 5.4.3 Results and Analysis 150

### 5.5 Discussion and Conclusions

References 154

### 6 Predictive Analytics: Classification in Medicine and Biology

_Eva K. Lee_

- 6.1 Introduction 159
- 6.2 Background 161
- 6.3 Machine Learning with Discrete Support Vector Machine Predictive Models 163
  - 6.3.1 Modeling of Reserved-Judgment Region for General Groups 164
  - 6.3.2 Discriminant Analysis via Mixed-Integer Programming 165
  - 6.3.3 Model Variations 167
  - 6.3.4 Theoretical Properties and Computational Strategies 170
- 6.4 Applying DAMIP to Real-World Applications 170
  - 6.4.1 Validation of Model and Computational Effort 171
  - 6.4.2 Applications to Biological and Medical Problems 171
- 6.5 Summary and Conclusion 182
  Acknowledgments 183
  References 183

### 7 Predictive Modeling in Radiation Oncology

_Hao Zhang, Robert Meyer, Leyuan Shi, Wei Lu, and Warren D’Souza_

- 7.1 Introduction 189
- 7.2 Tutorials of Predictive Modeling Techniques 191
  - 7.2.1 Feature Selection 191
  - 7.2.2 Support Vector Machine 192
  - 7.2.3 Logistic Regression 193
  - 7.2.4 Decision Tree 193
- 7.3 Review of Recent Predictive Modeling Applications in Radiation Oncology 194
  - 7.3.1 Machine Learning for Medical Image Processing 194
7.3.2 Machine Learning in Real-Time Tumor Localization 196
7.3.3 Machine Learning for Predicting Radiotherapy Response 197

7.4 Modeling Pathologic Response of Esophageal Cancer to Chemoradiotherapy 199
7.4.1 Input Features 200
7.4.2 Feature Selection and Predictive Model Construction 200
7.4.3 Results 202
7.4.4 Discussion 204

7.5 Modeling Clinical Complications after Radiation Therapy 205
7.5.1 Dose-Volume Thresholds: Relationship to OAR Complications 205
7.5.2 Modeling the Radiation-Induced Complications via Treatment Plan Surface 206
7.5.3 Modeling Results 208

7.6 Modeling Tumor Motion with Respiratory Surrogates 211
7.6.1 Cyberknife System Data 211
7.6.2 Modeling for the Prediction of Tumor Positions 212
7.6.3 Results of Tumor Positions Modeling 212
7.6.4 Discussion 214

7.7 Conclusion 215
References 215

8 Mathematical Modeling of Innate Immunity Responses of Sepsis: Modeling and Computational Studies 221
Chih-Hang J. Wu, Zhenzhen Shi, David Ben-Arieh, and Steven Q. Simpson

8.1 Background 221
8.2 System Dynamic Mathematical Model (SDMM) 223
8.3 Pathogen Strain Selection 224
8.3.1 Step 1: Kupffer Local Response Model 224
8.3.2 Step 2: Neutrophils Immune Response Model 228
8.3.3 Step 3: Damaged Tissue Model 233
8.3.4 Step 4: Monocytes Immune Response Model 234
8.3.5 Step 5: Anti-inflammatory Immune Response Model 237

8.4 Mathematical Models of Innate Immunity of AIR 239
8.4.1 Inhibition of Anti-inflammatory Cytokines 239
8.4.2 Mathematical Model of Innate Immunity of AIR 239
8.4.3 Stability Analysis 241

8.5 Discussion 247
8.5.1 Effects of Initial Pathogen Load on Sepsis Progression 247
8.5.2 Effects of Pro- and Anti-inflammatory Cytokines on Sepsis Progression 250

8.6 Conclusion 254
References 254
## PART II ANALYTICS FOR HEALTHCARE DELIVERY

### 9 Systems Analytics: Modeling and Optimizing Clinic Workflow and Patient Care

_Eva K. Lee, Hany Y. Atallah, Michael D. Wright, Calvin Thomas IV, Eleanor T. Post, Daniel T. Wu, and Leon L. Haley Jr_

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1 Introduction</td>
<td>264</td>
</tr>
<tr>
<td>9.2 Background</td>
<td>266</td>
</tr>
<tr>
<td>9.3 Challenges and Objectives</td>
<td>267</td>
</tr>
<tr>
<td>9.4 Methods and Design of Study</td>
<td>268</td>
</tr>
<tr>
<td>9.4.1 ED Workflow and Services</td>
<td>269</td>
</tr>
<tr>
<td>9.4.2 Data Collection and Time-Motion Studies</td>
<td>270</td>
</tr>
<tr>
<td>9.4.3 Machine Learning for Predicting Patient Characteristics and Return Patterns</td>
<td>274</td>
</tr>
<tr>
<td>9.4.4 The Computerized ED System Workflow Model</td>
<td>277</td>
</tr>
<tr>
<td>9.4.5 Model Validation</td>
<td>282</td>
</tr>
<tr>
<td>9.5 Computational Results, Implementation, and ED Performance Comparison</td>
<td>285</td>
</tr>
<tr>
<td>9.5.1 Phase I: Results</td>
<td>285</td>
</tr>
<tr>
<td>9.5.2 Phase I: Adoption and Implementation</td>
<td>288</td>
</tr>
<tr>
<td>9.5.3 Phase II: Results</td>
<td>288</td>
</tr>
<tr>
<td>9.5.4 Phase II: Adoption and Implementation</td>
<td>290</td>
</tr>
<tr>
<td>9.6 Benefits and Impacts</td>
<td>292</td>
</tr>
<tr>
<td>9.6.1 Quantitative Benefits</td>
<td>294</td>
</tr>
<tr>
<td>9.6.2 Qualitative Benefits</td>
<td>296</td>
</tr>
<tr>
<td>9.7 Scientific Advances</td>
<td>297</td>
</tr>
<tr>
<td>9.7.1 Hospital Care Delivery Advances</td>
<td>297</td>
</tr>
<tr>
<td>9.7.2 OR Advances</td>
<td>298</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>298</td>
</tr>
<tr>
<td>References</td>
<td>299</td>
</tr>
</tbody>
</table>

### 10 A Multiobjective Simulation Optimization of the Macrolevel Patient Flow Distribution

_Yunzhe Qiu and Jie Song_

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1 Introduction</td>
<td>303</td>
</tr>
<tr>
<td>10.2 Literature Review</td>
<td>305</td>
</tr>
<tr>
<td>10.2.1 Simulation Modeling on Patient Flow</td>
<td>305</td>
</tr>
<tr>
<td>10.2.2 Multiobjective Patient Flow Optimization Problems</td>
<td>306</td>
</tr>
<tr>
<td>10.2.3 Simulation Optimization</td>
<td>307</td>
</tr>
<tr>
<td>10.3 Problem Description and Modeling</td>
<td>308</td>
</tr>
<tr>
<td>10.3.1 Problem Description</td>
<td>308</td>
</tr>
<tr>
<td>10.3.2 System Modeling</td>
<td>310</td>
</tr>
</tbody>
</table>
10.4 Methodology
  10.4.1 Simulation Model Description
  10.4.2 Optimization
10.5 Case Study: Adjusting Patient Flow for a Two-Level Healthcare System Centered on the Puth
  10.5.1 Background and Data
  10.5.2 Simulation under Current Situation
  10.5.3 Model Validation
  10.5.4 Optimization through Algorithm 1
  10.5.5 Optimization through Algorithm 2
  10.5.6 Comparison of the Two Algorithms
  10.5.7 Managerial Insights and Recommendations
10.6 Conclusions and the Future Work
Acknowledgments
References

11 Analysis of Resource Intensive Activity Volumes in US Hospitals

Shivon Boodhoo and Sanchoy Das

11.1 Introduction
11.2 Structural Classification of Hospitals
11.3 Productivity Analysis of Hospitals
11.4 Resource and Activity Database for US Hospitals
  11.4.1 Medicare Data Sources for Hospital Operations
11.5 Activity-Based Modeling of Hospital Operations
  11.5.1 Direct Care Activities
  11.5.2 The Hospital Unit of Care (HUC) Model
  11.5.3 HUC Component Results by State
11.6 Resource use Profile of Hospitals from HUC Activity Data
  11.6.1 Comparing the Resource Use Profile of States
  11.6.2 Application of the Hospital Classification Rules
11.7 Summary
References

12 Discrete-Event Simulation for Primary Care Redesign: Review and a Case Study

Xiang Zhong, Molly Williams, Jingshan Li, Sally A. Kraft, and Jeffrey S. Sleeth

12.1 Introduction
12.2 Review of Relevant Literature
  12.2.1 Literature on Primary Care Redesign
  12.2.2 Literature on Discrete-Event Simulation in Healthcare
  12.2.3 UW Health Improvement Projects
12.3 A Simulation Case Study at a Pediatric Clinic 369
  12.3.1 Patient Flow 369
  12.3.2 Model Development 371
  12.3.3 Model Validation 376

12.4 What–If Analyses 376
  12.4.1 Staffing Analysis 376
  12.4.2 Resident Doctor 377
  12.4.3 Schedule Template Change 377
  12.4.4 Volume Change 379
  12.4.5 Room Assignment 379
  12.4.6 Early Start 380
  12.4.7 Additional Observations 382

12.5 Conclusions 382

References 382

13 Temporal and Spatiotemporal Models for Ambulance Demand 389
Zhengyi Zhou and David S. Matteson

13.1 Introduction 389

13.2 Temporal Ambulance Demand Estimation 391
  13.2.1 Notation 392
  13.2.2 Factor Modeling with Constraints and Smoothing 393
  13.2.3 Adaptive Forecasting with Time Series Models 395

13.3 Spatiotemporal Ambulance Demand Estimation 398
  13.3.1 Spatiotemporal Finite Mixture Modeling 400
  13.3.2 Estimating Ambulance Demand 403
  13.3.3 Model Performance 405

13.4 Conclusions 409

References 410

14 Mathematical Optimization and Simulation Analyses for Optimal Liver Allocation Boundaries 413
Naoru Koizumi, Monica Gentili, Rajesh Ganesan, Debasree DasGupta, Amit Patel, Chun-Hung Chen, Nigel Waters, and Keith Melancon

14.1 Introduction 414

14.2 Methods 416
  14.2.1 Mathematical Model: Optimal Locations of Transplant Centers and OPO Boundaries 416
  14.2.2 Discrete-Event Simulation: Evaluation of Optimal OPO Boundaries 422

14.3 Results 423
  14.3.1 New Locations of Transplant Centers 423
  14.3.2 New OPO Boundaries 426
  14.3.3 Evaluation of New OPO Boundaries 428
14.4 Conclusions 433
Acknowledgment 435
References 435

15 Predictive Analytics in 30-Day Hospital Readmissions for Heart Failure Patients 439
Si-Chi Chin, Rui Liu, and Senjuti B. Roy

15.1 Introduction 440
15.2 Analytics in Prediction Hospital Readmission Risk 441
15.2.1 The Overall Prediction Pipeline 441
15.2.2 Data Preprocessing 441
15.2.3 Predictive Models 442
15.2.4 Experiment and Evaluation 444
15.3 Analytics in Recommending Intervention Strategies 447
15.3.1 The Overall Intervention Pipeline 447
15.3.2 Bayesian Network Construction 448
15.3.3 Recommendation Rule Generation 452
15.3.4 Intervention Recommendation 453
15.3.5 Experiments 454
15.4 Related Work 457
15.5 Conclusion 459
References 459

16 Heterogeneous Sensing and Predictive Modeling of Postoperative Outcomes 463
Yun Chen, Fabio Leonelli, and Hui Yang

16.1 Introduction 463
16.2 Research Background 466
16.2.1 Acute Physiology and Chronic Health Evaluation (APACHE) 466
16.2.2 Simplified Acute Physiology Score (SAPS) 469
16.2.3 Mortality Probability Model (MPM) 470
16.2.4 Sequential Organ Failure Assessment (SOFA) 472
16.3 Research Methodology 474
16.3.1 Data Categorization 475
16.3.2 Data Preprocessing and Missing Data Imputation 475
16.3.3 Feature Extraction 482
16.3.4 Feature Selection 484
16.3.5 Predictive Model 487
16.3.6 Cross-Validation and Ensemble Voting Processes 489
16.4 Materials and Experimental Design 491
16.5 Experimental Results 491
CONTENTS

16.6 Discussion and Conclusions 498
Acknowledgments 499
References 499

17 Analyzing Patient–Physician Interaction in Consultation for Shared Decision Making 503
Thembi Mdluli, Joyatee Sarker, Carolina Vivas-Valencia, Nan Kong, and Cleveland G. Shields

17.1 Introduction 503
17.2 Literature Review 505
  17.2.1 Patient–Physician Interaction on Prognosis Discussion 506
  17.2.2 Physician–Patient Interaction on Pain Assessment 509
17.3 Our Recent Data Mining Studies 510
  17.3.1 Predicting Patient Satisfaction with Survey Data 510
  17.3.2 Predicting Patient Satisfaction with Conservation Data 513
17.4 Future Directions 515
  17.4.1 Regression Shrinkage and Selection 515
  17.4.2 Conversational Characterization 517
17.5 Concluding Remarks 519
References 520

18 The History and Modern Applications of Insurance Claims Data in Healthcare Research 523
Margrét V. Bjarndóttir, David Czerwinski, and Yihan Guan

18.1 Introduction 523
  18.1.1 Advantages and Limitations of Claims Data 525
  18.1.2 Application Areas 526
  18.1.3 Statistical Methodologies Used in Claims-Based Studies 528
18.2 Healthcare Cost Predictions 531
  18.2.1 Modeling of Healthcare Costs 531
  18.2.2 Modeling of Disease Burden and Interactions 533
  18.2.3 Performance Measures and Baselines 534
  18.2.4 Prediction Algorithms 534
  18.2.5 Applying Regression Trees to Cost Predictions 535
  18.2.6 Applying Clustering Algorithms to Cost Predictions 537
  18.2.7 Identifying High-Cost Members 539
  18.2.8 Discussion 539
18.3 Measuring Quality of Care 540
  18.3.1 Structure, Process, and Outcomes 540
  18.3.2 The Quality of Quality Data 542
  18.3.3 Composite Quality Measures 542
18.3.4 Practical Considerations for Constructing Quality Scores 544
18.3.5 A Statistical Approach to Measuring Quality 545
18.3.6 Quality as a Case Management Tool 546
18.3.7 Discussion 547
18.4 Conclusions 548
References 548

19 Understanding the Role of Social Media in Healthcare via Analytics: a Health Plan Perspective 555
Sinjini Mitra and Rema Padman
19.1 Introduction 555
19.2 Literature Review 556
19.2.1 Privacy and Security Concerns in Social Media and Healthcare 559
19.2.2 Analytics in Healthcare and Social Media 561
19.3 Case Study Description 562
19.3.1 Survey Design 563
19.4 Research Methods and Analytics Tools 564
19.4.1 The Logistic Regression Model 564
19.5 Results and Discussions 568
19.5.1 Descriptive Statistics 568
19.5.2 Baseline of Technology Usage 570
19.5.3 Mobile and Social Media Usage 571
19.5.4 Clustering of Member Population by Technology, Social, and Mobile Media Usage 572
19.5.5 Interest in Adopting Online Tools for Healthcare Purposes 573
19.5.6 Interest in Adopting Mobile Apps for Healthcare Purposes 574
19.5.7 Health and Wellness Objectives 577
19.5.8 Privacy and Security Concerns 580
19.5.9 Predictive Models 581
19.6 Conclusions 584
References 585

INDEX 589