

Contents

List of Figures

xxi

List of Tables

xxv

Symbol Description

xxvii

I Basic Concepts

1

1	Ontologies and Applications of Ontologies in Biomedicine	3
1.1	What Is an Ontology?	3
1.2	Ontologies and Bio-Ontologies	5
1.3	Ontologies for Data Organization, Integration, and Searching	6
1.4	Computer Reasoning with Ontologies	9
1.5	Typical Applications of Bio-Ontologies	10
2	Mathematical Logic and Inference	11
2.1	Representation and Logic	11
2.2	Propositional Logic	13
2.3	First-Order Logic	18
2.4	Sets	25
2.5	Description Logic	29
2.5.1	Description Language \mathcal{AL}	29
2.5.2	Description Language \mathcal{ALC}	31
2.5.3	Further Description Logic Constructors	32
2.6	Exercises and Further Reading	36
3	Probability Theory and Statistics for Bio-Ontologies	41
3.1	Probability Theory	41
3.1.1	Hypothesis Testing	43
3.1.2	p -Values and Probability Distributions	44
3.1.3	Multiple-Testing Correction	51
3.2	Bayes' Theorem	56
3.3	Introduction to Graphs	58
3.4	Bayesian Networks	62
3.5	Exercises and Further Reading	64

4 Ontology Languages	67
4.1 OBO	67
4.1.1 OBO Stanzas	68
4.1.2 Intersections: Computable Definitions	70
4.2 OWL and the Semantic Web	71
4.2.1 Resource Description Framework	72
4.2.2 RDF Schema	78
4.2.3 The Web Ontology Language OWL	85
4.2.4 OBO, RDF, RDFS, and OWL	95
4.3 Exercises and Further Reading	99
II Bio-Ontologies	113
5 The Gene Ontology	115
5.1 A Tool for the Unification of Biology	115
5.2 Three Subontologies	117
5.2.1 Molecular Function	117
5.2.2 Biological Process	117
5.2.3 Cellular Component	118
5.3 Relations in GO	120
5.4 GO Annotations	121
5.4.1 Evidence for Gene Functions	124
5.4.2 Inferred from Electronic Annotation	127
5.4.3 The True Path Rule and Propagation of Annotations .	128
5.5 GO Slims	133
5.6 Exercises and Further Reading	134
6 Upper-Level Ontologies	139
6.1 Basic Formal Ontology	139
6.2 The Big Divide: Continuants and Occurrents	140
6.2.1 Continuants	141
6.2.2 Occurrents	142
6.3 Universals and Particulars	142
6.4 Relation Ontology	143
6.5 Revisiting Gene Ontology	147
6.6 Revisiting GO Annotations	148
6.7 Exercises and Further Reading	150
7 A Selective Survey of Bio-Ontologies	153
7.1 OBO Foundry	153
7.2 The National Center for Biomedical Ontology	155
7.3 Bio-Ontologies	155
7.3.1 Ontologies for Anatomy: The FMA and Model Organisms	156
7.3.2 Cell Ontology	159
7.3.3 Chemical Entities of Biological Interest	160

7.3.4	OBI	162
7.3.5	The Protein Ontology	162
7.3.6	The Sequence Ontology	165
7.3.7	Mammalian Phenotype Ontology (MPO)	166
7.3.8	Human Phenotype Ontology (HPO)	167
7.3.9	MPATH	171
7.3.10	PATO	172
7.4	What Makes a Good Ontology?	175
7.5	Exercises and Further Reading	177
III	Graph Algorithms for Bio-Ontologies	179
8	Overrepresentation Analysis	181
8.1	Definitions	182
8.2	Term-for-Term	183
8.3	Multiple Testing Problem	185
8.4	Term-for-Term Analysis: An Extended Example	188
8.5	Inferred Annotations Lead to Statistical Dependencies in Ontology DAGs	192
8.6	Parent-Child Algorithms	195
8.7	Parent-Child Analysis: An Extended Example	198
8.8	Topology-Based Algorithms	200
8.8.1	Elim	200
8.8.2	Weight	202
8.9	Topology-elim: An Extended Example	205
8.10	Other Approaches	207
8.11	Summary	209
8.12	Exercises and Further Reading	209
9	Model-Based Approaches to GO Analysis	219
9.1	A Probabilistic Generative Model for GO Enrichment Analysis	219
9.2	A Bayesian Network Model	222
9.2.1	Maximum a posteriori	226
9.2.2	Monte Carlo Markov Chain Algorithm	227
9.2.3	MGSA Algorithm with Unknown Parameters	230
9.3	MGSA: An Extended Example	233
9.4	Summary	234
9.5	Exercises and Further Reading	235
10	Semantic Similarity	237
10.1	Information Content in Ontologies	237
10.2	Semantic Similarity of Genes and Other Items Annotated by Ontology Terms	247
10.2.1	Graph-Based and Set-Based Measures of Semantic Similarity	248
10.2.2	Applications of Semantic Similarity in Bioinformatics	249

10.2.3 Applications of Semantic Similarity for Clinical Diagnostics	251
10.3 Statistical Significance of Semantic Similarity Scores	252
10.4 Exercises and Further Reading	255
11 Frequency-Aware Bayesian Network Searches in Attribute Ontologies	261
11.1 Modeling Queries	262
11.1.1 High-Level Description of the Model	262
11.1.2 Annotation Propagation Rule for Bayesian Networks .	264
11.1.3 LPDs of Hidden Term States	266
11.1.4 LPDs of Observed Term States	266
11.2 Probabilistic Inference for the Items	270
11.3 Parameter-Augmented Network	272
11.4 The Frequency-Aware Network	273
11.5 Benchmark	274
IV Inference in Ontologies	279
12 Inference in the Gene Ontology	281
12.1 Inference over GO Edges	281
12.2 Cross-Products and Logical Definitions	285
12.2.1 Intra-GO Cross-Product Definitions	286
12.2.2 External Cross-Product Definitions	288
12.2.3 Reasoning with Cross-Product Definitions	288
12.3 Exercises and Further Reading	289
13 RDFS Semantics and Inference	293
13.1 Definitions	293
13.2 Interpretations	294
13.3 RDF Entailment	303
13.4 RDFS Entailment	305
13.5 Entailment Rules	307
13.6 Summary	314
13.7 Exercises and Further Reading	314
14 Inference in OWL Ontologies	317
14.1 The Semantics of Equality	317
14.2 The Semantics of Properties	320
14.3 The Semantics of Classes	325
14.4 The Semantics of the Schema Vocabulary	331
14.5 Conclusions	333
14.6 Exercises and Further Reading	333

15 Algorithmic Foundations of Computational Inference	335
15.1 The Tableau Algorithm	336
15.1.1 Negative Normal Form	338
15.1.2 Algorithm for ABox	339
15.1.3 Adding Support for the TBox	344
15.2 Developer Libraries	346
15.3 Exercises and Further Reading	348
16 SPARQL	357
16.1 SPARQL Queries	357
16.2 Combining RDF Graphs	365
16.3 Conclusions	368
16.4 Exercises and Further Reading	369
Appendices	375
A An Overview of R	377
B Information Content and Entropy	395
C W3C Standards: XML, URIs, and RDF	399
D W3C Standards: OWL	427
Glossary	457
Bibliography	461
Index	485
4.1 Graphs: The Representation of a Collection of RDF Triple	102
4.2 Graphing the Representation of a Collection of RDF Triple	103
4.3 Extraction of RDF Statements in an RDF Graph	103
4.4 Extracting Information from an RDF Graph	103
4.5 Prefixes	104
4.6 Prefixes Tutorial	106
4.7 Prefixes Tutorial	108
5.1 Multiple Expressions: Abstraction of Cycloids	116
5.2 Annotations: Expressions Using λ -Terms	121
5.3 A Visualizing of the Stark Rule	121
5.4 A Formalization of the Stark Rule	122
5.5 GO Rule: Applications by the Stark Rule	123
6.1 A Simplified View of the RDF	143
6.2 Definition of Terms in the Relation Ontology	145
6.3 Definition of Terms in the Relation Ontology	146
7.1 -Cal Type Theory	161