

#### **4444**6667

# **Contents**

#### Plan of the book xix

1	In	tro	di	ictic	n ·
	1113		98 E E I		,,,

Life in space and time 3

Evolution is the change over time in the world of living things 4

Dogmas: central and peripheral 6

Observables and data archives 9

Information flow in bioinformatics 12

Curation, annotation, and quality control 13

The World Wide Web 14

Electronic publication 15

Computers and computer science 16

Programming 17

Biological classification and nomenclature 21

Use of sequences to determine phylogenetic relationships 24

Use of SINES and LINES to derive phylogenetic relationships 30

Searching for similar sequences in databases: PSI-BLAST 32

Introduction to protein structure 40

The hierarchical nature of protein architecture 41

Classification of protein structures 44

Protein structure prediction and engineering 51

Critical Assessment of Structure Prediction (CASP) 52

Protein engineering 52

Proteomics 52

DNA microarrays 53

Mass spectrometry 54

Systems biology 54

Clinical implications 55

The future 57

Recommended reading 57

Exercises, Problems, and Weblems 59

# 2 Genome organization and evolution 67

Genomes and proteomes 68

Genes 69

Proteomes 71

# Eavesdropping on the transmission of genetic information 72

Mappings between the maps 77 High-resolution maps 78

## Picking out genes in genomes 80

#### Genomes of prokaryotes 81

The genome of the bacterium Escherichia coli 82

The genome of the archaeon Methanococcus jannaschii 85

The genome of one of the simplest organisms: Mycoplasma genitalium 86

#### Genomes of eukaryotes 87

The genome of Saccharomyces cerevisiae (baker's yeast) 89

The genome of Caenorhabditis elegans 93

The genome of Drosophila melanogaster 94

The genome of Arabidopsis thaliana 95

## The genome of Homo sapiens (the human genome) 96

Protein coding genes 97

Repeat sequences 99

**RNA 100** 

# Single-nucleotide polymorphisms (SNPs) 101

#### Genetic diversity in anthropology 102

Genetic diversity and personal identification 103

Genetic analysis of cattle domestication 104

#### Evolution of genomes 104

Please pass the genes: horizontal gene transfer 108

Comparative genomics of eukaryotes 109

Recommended reading 111

Exercises, Problems, and Weblems 112

# 3 Archives and information retrieval 117

#### Introduction 118

Database indexing and specification of search terms 118

Follow-up questions 120

Analysis of retrieved data 121

#### The archives 121

Nucleic acid sequence databases 122

Genome databases 124

Protein sequence databases 124

Databases of structures 128

Specialized, or boutique databases 135

Expression and proteomics databases 136

Databases of metabolic pathways 138

Bibliographic databases 139

Surveys of molecular biology databases and servers 139

#### Gateways to archives 140

Access to databases in molecular biology 141

ENTREZ 141

The Sequence Retrieval System (SRS) 148

The Protein Identification Resource (PIR) 149

ExPASy—Expert Protein Analysis System 150

Ensembl 151

#### Where do we go from here? 152

Recommended reading 152

Exercises, Problems, and Weblems 153

# 4 Alignments and phylogenetic trees 157

Introduction to sequence alignment 158

The dotplot 160

Dotplots and sequence alignments 165

Measures of sequence similarity 171

Scoring schemes 171

# Computing the alignment of two sequences 175

Variations and generalizations 175

Approximate methods for quick screening of databases 176

# The dynamic programming algorithm for optimal pairwise sequence alignment 176

Significance of alignments 182

Multiple sequence alignment 186

# Applications of multiple sequence alignments to database searching 188

Profiles 189

PSI-BLAST 191

Hidden Markov Models 193

Phylogeny 198

#### Phylogenetic trees 203

Clustering methods 205

Cladistic methods 206

The problem of varying rates of evolution 207

Computational considerations 208

Recommended reading 209

Exercises, Problems, and Weblems 210

# 5 Protein structure and drug discovery 219

Introduction 220

#### Protein stability and folding 223

The Sasisekharan-Ramakrishnan-Ramachandran plot describes allowed mainchain conformations 223

The sidechains 225

Protein stability and denaturation 225

Protein folding 228

# Applications of hydrophobicity 229

Superposition of structures, and structural alignments 233

DALI (Distance-matrix ALIgnment) 235

#### **Evolution of protein structures** 236

## Classifications of protein structures 238

**SCOP 239** 

#### Protein structure prediction and modelling 240

Critical Assessment of Structure Prediction (CASP) 242

Secondary structure prediction 244

Homology modelling 250

Fold recognition 252

Conformational energy calculations and molecular dynamics 255

ROSETTA 259

**LINUS 259** 

# Assignment of protein structures to genomes 263

### Prediction of protein function 265

Divergence of function: orthologues and paralogues 266

## Drug discovery and development 269

The lead compound 271

Bioinformatics in drug discovery and development 273

Recommended reading 284

Exercises, Problems, and Weblems 285

# 6 Proteomics and systems biology 291

### **DNA microarrays** 293

Analysis of microarray data 295

#### Mass spectrometry 301

Identification of components of a complex mixture 301

Protein sequencing by mass spectrometry 304

Genome sequence analysis by mass spectrometry 306

# Systems biology 311

### Networks and graphs 313

Network structure and dynamics 318

#### Protein complexes and aggregates 320

Properties of protein-protein complexes 321

#### Protein interaction networks 324

#### Regulatory networks 329

Structures of regulatory networks 330

Structural biology of regulatory networks 336

Recommended reading 339

Exercises, Problems, and Weblems 339

#### Conclusions 345

**Answers to Exercises** 347

Glossary 353

Index 357

Colour plates