CONTENTS

| Prote evolution: divergence of sequences and structures | |
|--|------|
| Preface | vii |
| Plan of the third edition | × |
| Recommended reading | xiii |
| Introduction to genomics on the web | xiii |
| Acknowledgements | xiv |
| List of abbreviations | xxv |
| Genomics and computing | |
| Introduction and Background | 1 |
| Learning goals | 1 |
| Genomics: the hub of biology | 2 |
| Phenotype = genotype + environment + life history + epigenetics | 2 |
| Varieties of genome organization | 4 |
| Chromosomes, organelles, and plasmids | 4 |
| Genes | 6 |
| The scope and applications of genome sequencing projects | 9 |
| Variations in genome sequences within species | 10 |
| Mutations and disease | 10 |
| Single-nucleotide polymorphisms Haplotypes | 10 |
| A clinically important haplotype: the major histocompatibility complex | 14 |
| Populations Populations | 15 |
| Species assumed one colmono D | 17 |
| The biosphere | 18 |
| Extinctions gazagib to notifiever9 | 19 |
| The future? | 22 |
| Genome projects and our current library of genome information | 25 |
| High-throughput sequencing | 25 |
| De novo sequencing | 26 |
| Resequencing | 26 |
| Exome sequencing | 26 |
| what's in a genome? | 27 |
| Some regions of the genome encode non-protein-coding RNA molecules | 28 |
| Other regions contain binding sites for ligands responsible for regulation | 28 |
| of transcription | 29 |
| Repetitive elements of unknown function account for surprisingly large | |
| fractions of our genomes | 29 |
| Dynamic components of genomes | 30 |
| Genomics and developmental biology | 32 |
| Genes and minds: neurogenomics | 35 |
| Genetics of behaviour | 36 |

| | Proteomics | | 37 |
|---|---|------------------|----------------|
| | Protein evolution: divergence of sequences and structures within and among species | | 39 |
| | Mechanisms of protein evolution | | 39 |
| | Organization and regulation | | 42 |
| | Some mechanisms of regulation act at the level of transcription | Recommended | 45 |
| | Some mechanisms of regulation act at the level of translation Some regulatory mechanisms affect protein activity | | 45 47 |
| | On the web: genome browsers | | 47 |
| | Genomics and computing | | 52 |
| | Archiving and analysis of genome sequences and related data Databanks in molecular biology Programming | | 52 53 54 |
| | Looking forward | | 55 |
| | Recommended reading | | 55 |
| | Exercises and problems | Chromosomas, er | 57 |
| 2 | The Human Genome Project: Achievements and App | olications | 62 |
| | Learning goals | | 62 |
| | ' the end of the beginning' | | 63 |
| | Human genome sequencing | | 66 |
| | What makes us human? | | 67 |
| | Comparative genomics Genomics and language | | 68 68 |
| | The human genome and medicine | | 71 |
| | Prevention of disease | | 71 |
| | Detection and precise diagnosis | | 72 |
| | Genetic counselling—carrier status | | 72 |
| | Tunable healthcare delivery: pharmacogenomics | | 72 |
| | 'Pop' applications of genome sequencing | | 76 |
| | Genomics in personal identification | | 76 |
| | DNA 'fingerprinting' | | 77 |
| | Personal identification by amplification of specific regions has superseded the RFLP approach | | 79 |
| | Mitochondrial DNA | | 79 |
| | Analysis of non-human DNA sequences Parentage testing | | 82 82 |
| | Thisel logal and social issues | fractions of our | 05 |
| | Databases containing human DNA services is formation | | 05 |
| | Use of DNA sequencing in research on human subjects | | 88 |
| | Looking forward | | 88 |
| | Recommended reading | | 88 |
| | Exercises and problems | | 90 |

| and a second | |
|--|--------------------------------------|
| earning goals | Learning Soals |
| lassical genetics as background | Evolution is exploration |
| What is a gene? | |
| Naps and tour guides | |
| Genetic maps | |
| Linkage | |
| Linkage disequilibrium | Puttern matching-the basic tool |
| Restriction maps | |
| iscovery of the structure of DNA | |
| NA sequencing | |
| NA sequencing | Varieties and extensions |
| DNA sequencing by termination of chain replic | ation |
| The Maxam-Gilbert chemical cleavage method | |
| Automation of DNA sequencing | Evolution of protein structure and |
| organizing a large-scale sequencing project | Phylogeny |
| Bring on the clones: hierarchical—or 'BAC-to-B | AC'—genome |
| sequencing | Charles including evolution: genetic |
| Whole-genome shotgun sequencing | |
| ext-generation sequencing | |
| Roche 454 Life Sciences | |
| Illumina | |
| Ion Torrent/Personal Genome Machine (PGM) | |
| Oxford Nanopore | |
| 10X Genomics | |
| The Bionano Irys system | |
| fe in the fast lane | |
| How much sequencing power is there in the wo | orld? |
| atabanks in molecular biology | Genome orzanization in prokarvo |
| Nucleic acid sequence databases | |
| Protein sequence databases | |
| Databases of genetic diseases-OMIM and OM | Archaea |
| Databases of structures | |
| Specialized or 'boutique' databases | |
| Expression and proteomics databases | |
| Bibliographic databases | |
| Surveys of molecular biology databases and ser | vers |
| omputer programming in genomics | Genomics and the development of |
| Programming languages | |
| ow to compute effectively | |
| oking forward | |
| Commended and the | |
| commended reading | |
| ercises and problems | |

| 4. | Evolution and Genomic Change | | 143 |
|----|--|-----------------------------|-----|
| | Learning goals | | 143 |
| | Evolution is exploration | | 144 |
| | Biological systematics | | 146 |
| | Biological nomenclature | | 146 |
| | Measurement of biological similarities and differences | | 148 |
| | Homologues and families | | 150 |
| | Pattern matching_the basic tool of bioinformatics | | 151 |
| | Converse alignment | | 151 |
| | Defining the ontimum alignment | | 153 |
| | Scoring schemes | | 155 |
| | Varieties and extensions | | 157 |
| | Approximate methods for quick screening of databases | | 158 |
| | Pattern matching in three-dimensional structures | | 160 |
| | Evolution of protein sequences, structures, and function | S and Traditio-miskaW off | 161 |
| | Evolution of protein structure and function | upas Avid to noor-out u- | 164 |
| | Phylogeny | | 165 |
| | Calculation of phylogenetic trees | Bring on the different many | 169 |
| | Short-circuiting evolution: genetic engineering | | 173 |
| | Looking forward | | 175 |
| | Recommended reading | | 176 |
| | Exercises and problems | | 177 |
| | me Madrine (PCAN) | | |
| | | | 170 |
| 5 | Genomes of Prokaryotes and Viruses | | 179 |
| | Learning goals | | 179 |
| | Evolution and phylogenetic relationships in prokary | votes | 180 |
| | Major types of prokaryotes | | 180 |
| | Do we know the root of the tree of life? | | 182 |
| | Genome organization in prokaryotes | | 183 |
| | Replication and transcription | | 184 |
| | Gene transfer | | 184 |
| | Archaea The genome of Methanococcus jannaschii | | 186 |
| | Life at extreme temperatures | | 188 |
| | Comparative genomics of hyperthermophilic archaea: | | |
| | Thermococcus kodakarensis and pyrococci | | 189 |
| | Bacteria | | 194 |
| | Genomes of pathogenic bacteria | | 195 |
| | Genomics and the development of vaccines | | 197 |
| | Viruses | | 198 |
| | Nucleocytoplasmic large DNA viruses (or giant viruses) | | 199 |
| | Viral genomes | | 199 |
| | Recombinant viruses | | 199 |
| | Viruses and evolution | | 201 |
| | innuenza: a past and current threat | | 201 |

| Marine cyanobacteria—an in-depth study | Snamut anion tona |
|--|---------------------------------------|
| Looking forward | Comparative genomic |
| Recommended reading | |
| Recommended reading | |
| Exercises and problems | |
| when have transfer hand Denisovan Ski | |
| Genomes of Eukaryotes | |
| Learning goals | |
| The origin and evolution of eukaryotes | |
| Evolution and phylogenetic relationships in | eukaryotes |
| The yeast genome | |
| The evolution of plants | |
| The Arabidopsis thaliana genome | The Impact of Genome Sequen |
| Genomes of animals | |
| The genome of the sea squirt (Ciona intestina | lis) |
| The genome of the pufferfish (Tetraodon nigr | oviridis) |
| The genome of the chicken (Gallus gallus dom | nesticus) |
| The genome of the dog | s anatinus) |
| Pelacesequencing ancient DNA | |
| Palaeosequencing—ancient DNA | |
| Recovery of DNA from ancient samples | |
| High-throughput sequencing of mammoth DN | Identification of genes associated AL |
| The phylogeny of elephants | |
| Looking forward | |
| Recommended reading | |
| Exercises and problems | |
| Misserres Life are femicuantitative | |
| Composition Composition | |
| comparative Genomics | |
| Learning goals | |
| Introduction | |
| Unity and diversity of life | |
| Taxonomy based on sequences | |
| Sizes and organization of genomes | |
| Genome sizes | |
| Genome organization in eukaryotes | |
| Photosynthetic sea slugs: endosymbiosis of ch | oroplasts |
| How genomes differ | Exercises and problems an encircler |
| Variation at the level of individual nucleotides | |
| Duplications | |
| Duplication of genes | |

| 2 | ۰ | ٠ | |
|---|---|---|--|
| 1 | ъ | ٠ | |
| | - | | |

| Family expansion: G protein-coupled receptors | Ome, 'ome, on the ranger metag |
|--|-----------------------------------|
| Comparisons at the chromosome level: synten | |
| What makes us human? | |
| Comparative genomics | |
| Genomes of chimpanzees and humans | |
| Genomes of mice and rats | |
| Model organisms for study of human diseas | ses |
| The genome of Caenorhabditis elegans | |
| The genome of <i>Drosophila melanogaster</i> | |
| Homologous genes in numans, worms, and his | eleog guimes. |
| Looking forward | |
| Recommended reading | |
| Exercises and problems | |
| | |
| The Impact of Genome Sequences on H | uman |
| Health and Disease | Genomes of animals |
| learning goals | |
| Introduction | |
| | The genome of the chicken (Calibo |
| Some diseases are associated with mutation | is in specific genes |
| Haemoglobinopathies—molecular diseases cau | ised by abnormal |
| Phenylketonuria | |
| Alzheimer's disease | |
| Identification of genes associated with inherite | d diseases |
| Genome-wide association studies | |
| GWAS of sickle-cell disease | |
| GWAS of type 2 diabetes | |
| GWAS of schizophrenia | |
| The human microbiome | |
| Treatment of abnormal microbiome composition | n |
| Cancer genomics | |
| SNPs and cancer | |
| Whole-genome sequencing association studies | of breast cancer |
| Copy-number alterations in cancer | |
| Chromosomal aberrations | |
| microRNAs and cancer | |
| Immunotherapy for cancer | |
| Looking forward | |
| Recommended reading | |
| Exercises and problems | |
| | |
| | |
| | |
| | |

| earning goals | Development of ambiotic resistance in b |
|--|---|
| Ancestry of Homo sapiens | |
| The Neanderthal genome | |
| The Denisovan genome | Looking forward |
| What do these data tell us? | Recommended reading |
| What have Neanderthais and Denisovan | is done for us lately? |
| Ancient populations and migrations | have needed and |
| Western civilization? I think it would | be a good idea |
| Domestication of the dog | |
| Domestication of the horse | |
| Domestication of crops | |
| Maize (Zea mays) | |
| Rice (Oryza sativa) | |
| Control of flowering time | |
| Chocolate (Theobroma casa) | |
| The Theobroma cacao) | |
| The Theobroma cacao genome | |
| Looking forward | Post-translational modifications |
| Recommended reading | |
| Exercises and problems | |
| | |
| Franscriptomics | |
| Learning goals | wards special many |
| ntroduction | |
| Microarrays | |
| Microarray data are semiquantitative | |
| Applications of DNA microarrays | |
| Analysis of microarray data | |
| RNAseq | |
| RNAseq versus microarrays | |
| expression patterns in different physio | logical states |
| Sleep in rats and fruit flies | |
| xpression pattern changes in develop | ment opin notosis subregnet-woll |
| Variation of expression patterns during the | he life cycle of |
| Drosophila melanogaster | |
| Drosophila melanogaster Flower formation in roses | |

| | Evolutionary changes in expression patterns | | 351 |
|----|--|----------------------------|------------|
| | Applications of transcriptomics in medicine | | 353 |
| | Development of antibiotic resistance in bacteria Childhood leukaemias | | 353 |
| | The Encyclopedia of DNA Elements (ENCODE) | | 357 |
| | Looking forward | | 355 |
| | Percommended reading | | 305 |
| | Exercises and problems | | 360 |
| | exercises and problems | | 361 |
| - | there are a good toos of around the second to a | | 1 |
| 11 | Proteomics | | 363 |
| | Learning goals | | 363 |
| | Introduction | | 364 |
| | Protein nature and types of proteins | | 364 |
| | Protein structure | | 365 |
| | The chemical structure of proteins | Control of Bowering time | 365 |
| | Conformation of the polypeptide chain | | 367 |
| | Protein folding patterns | | 367 |
| | Disorder in proteins | | 370 |
| | Post-translational modifications | | 372 |
| | Why is there a common genetic code with 20 ca | nonical amino acids? | 374 |
| | Separation and analysis of proteins | Exercises and problems | 375 |
| | Polyacrylamide gel electrophoresis (PAGE) | | 375 |
| | Two-dimensional PAGE | | 375 |
| | Mass spectrometry | | 376 |
| | Identification of components of a complex mixture | | 377 |
| | Protein sequencing by mass spectrometry | | 378 |
| | Quantitative analysis of relative abundance | | 378 |
| | Measuring deuterium exchange in proteins | | 379 |
| | Experimental methods of protein structure deter | mination | 381 |
| | X-ray crystallography of proteins | | 381 |
| | Interpretation of the electron density: model building How accurate are the structures? | g and improvement | 383 384 |
| | NMR spectroscopy in structural biology | | 386 |
| | Protein structure determination by NMR | | 386 |
| | Low-temperature electron microscopy (cryoEM) Classifications of protein structures | Expression pattern changes | 387 388 |
| | SCOP | | 389 |
| | SCOP2 | | 391 |
| | Protein complexes and aggregates | | 391 |
| | Protein aggregation diseases | | 392 |
| | Properties of protein-protein complexes | | 393 |
| | Stoichiometry-what is the composition of the comp | blex? | 393 |
| | Affinity—how stable is the complex? | | 394 |

| | How are complexes organized in three dimensions? Multisubunit proteins | 395 396 |
|----|--|------------|
| | Many proteins change conformation as part of the mechanism of their function | 396 |
| | Conformational change during enzymatic catalysis Motor proteins | 397 399 |
| | Allosteric regulation of protein function | 401 |
| | Allosteric changes in haemoglobin | 402 |
| | Conformational states of serine protease inhibitors (serpins) | 404 |
| | Protein structure prediction and modelling | 405 |
| | Homology modelling | 406 |
| | Secondary structure prediction Prediction of novel folds: ROSETTA | 408 |
| | Available protocols for protein structure prediction | 409 |
| | Structural genomics | 411 |
| | Directed evolution and protein design | 412 |
| | Directed evolution of subtilisin E | 412 |
| | Looking forward | 414 |
| | Recommended reading | 414 |
| | Exercises and problems | 415 |
| | regulation a start way a share a start and a start and a start | |
| 12 | Metabolomics | 419 |
| | Learning goals | 419 |
| | Introduction | 419 |
| | Classification and assignment of protein function | 420 |
| | The Enzyme Commission | 420 |
| | The Gene Ontology™ Consortium protein function classification Comparison of EC and GO classifications | 421 423 |
| | Metabolic networks | 424 |
| | Databases of metabolic pathways | 425 |
| | EcoCyc | 425 |
| | The Kyoto Encyclopedia of Genes and Genomes | 427 |
| | The Human Metabolome Database | 428 |
| | Evolution and phylogeny of metabolic pathways | 429 |
| | Alignment and comparison of metabolic pathways | 431 |
| | Comparing linear metabolic pathways Reconstruction of metabolic networks Comparing non-linear metabolic pathways: the pentose phosphate | 432 432 |
| | Mothe Lemine in the Calvin–Benson cycle | 434 |
| | Dynamia mark the state to the state of the s | 435 |
| | Looking formed by the second s | 437 |
| | Possesses la la sta | 439 |
| | Exercises and the second secon | 439 |
| | exercises and problems | 441 |

| 13 | Systems Biology | 443 |
|-------|--|------------|
| | Learning goals | 443 |
| | Introduction | 444 |
| | Regulatory mechanisms | 444 |
| - 995 | Two parallel networks: physical and logical | 445 |
| | Networks and graphs | 446 |
| | Robustness and redundancy | 447 |
| | Connectivity in networks | 448 |
| | Dynamics, stability, and robustness | 449 |
| | Protein complexes and aggregates | 451 |
| | Protein interaction networks | 451 |
| | Protein-DNA interactions | 456 |
| | DNA-protein complexes | 456 |
| | Structural themes in protein–DNA binding and sequence recognition | 457 |
| | Bacteriophage T7 DNA polymerase | 458 |
| | Some protein-DNA complexes that regulate gene transcription | 459 |
| | Regulatory networks | 463 |
| | Structures of regulatory networks Structural biology of regulatory networks | 464 465 |
| | Gene regulation | 466 |
| | The transcriptional regulatory network of Escherichia coli | 466 |
| | The genetic switch of bacteriophage λ | 469 |
| | Regulation of the lactose operon in <i>Escherichia coli</i> | 472 |
| | Adaptability of the yeast regulatory network | 474 |
| | Looking forward | 479 |
| | Recommended reading | 479 |
| | Exercises and problems | 480 |
| | Excretises and problems | 400 |
| | E ili and a communication ange in proteins | |
| | Epilogue | 483 |
| | Index | 404 |
| | The Human Metabolome Database | 455 |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |