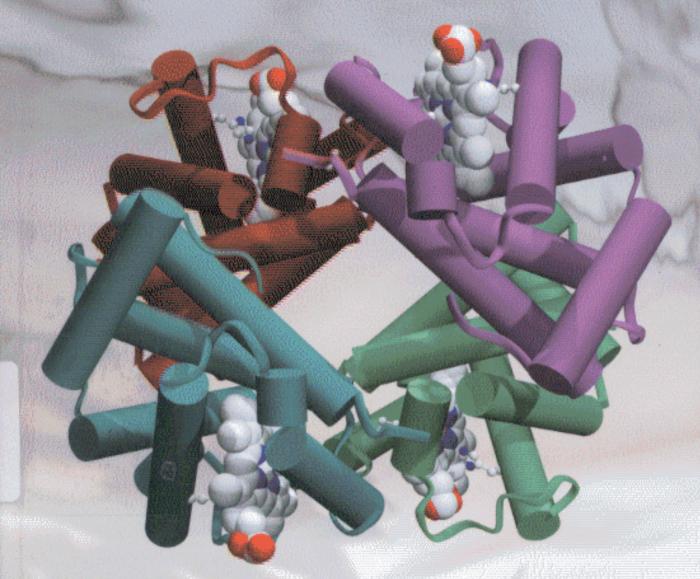
INTRODUCTION TO

PROTEIN SCIENCE

Architecture, Function, and Genomics



ARTHUR M. LESK

PREFACE		XIII
1	THE RIBOSOME—THE FULCRUM OF GENOMICS	1
	Introduction	1
	Structural studies of ribsomes by X-ray crystallography and electron microscopy	3
	The genetic code	5
	The biological context of protein synthesis—the basis of evolution	7
	Regulation	9
	USEFUL WEB SITES	10
	RECOMMENDED READING	10
	EXERCISES, PROBLEM, AND WEBLEM	11
2	GENOMICS AND PROTEOMICS	13
	Genome sequences	14
	Gene sequences determine amino acid sequences	15
	Amino acid sequences determine protein structures	19
	Secondary structure	21
	Tertiary and quaternary structure	22
	Protein stability and denaturation	22
	A survey of protein structures and functions	24
	Fibrous proteins	25
	Enzymes—proteins that catalyse chemical reactions	28
	Antibodies	31
	Inhibitors	31 32
	Carrier proteins	32
		35
	Receptors Regulatory proteins	36
	Motor proteins	39
	Protein folding patterns	39
	Folding patterns in native proteins—themes and variations	43
	Modular structure of proteins	44
	Protein evolution	46
	How do proteins develop new functions?	48
	Integration and control of protein function	48

...

CONTENTS

	Protein expression patterns in space and time: proteomics	52
	Subcellular localization	- 52
	Protein turnover	53
	DNA microarrays	54
	Mass spectrometry	57
	Computing in protein science	62
	Computer-based instrumentation	62
	Simulations, including molecular dynamics	63
	Molecular graphics Bioinformatics	64
		65
	USEFUL WEB SITES RECOMMENDED READING	67
		68
	EXERCISES, PROBLEMS, AND WEBLEMS	68
3	THE CHEMICAL STRUCTURE AND ACTIVITY OF PROTEINS	73
	The polypeptide chain and protein conformation	74
	The amino acids	74
	Protein main chain conformation	77
	Side chain conformation	79
	Rotamer libraries	80
	Stabilization of the native state	80
	Spectroscopic methods of characterizing proteins in solution	
	Absorbance and fluorescence of proteins	86
	Fluorescence is sensitive to the environment and dynamics of	89
	the chromophore	90
	Fluorescence resonance energy transfer (FRET)	91
	Circular dichroism	91
	Protein structure determination	93
	X-ray crystallography	95
	Nuclear magnetic resonance spectroscopy (NMR) Low-temperature electron microscopy (cnocEM)	97
	(Clybelvi)	98
	The relationship between structure determinations of isolated proteins, and protein structure and function in vivo	99
	Protein-ligand interactions	100
	Catalysis by enzymes	
	The Michaelis-Menten equation describes the velocity of enzymatic	102
	reactions as a function of substrate concentration	102
	Conformational change	104
	The sliding filament mechanism of muscle contraction	104
	Control of protein activity	106
	-	100

		CONTENTS
	Control of protein function: allosteric regulation	109
	The allosteric change of haemoglobin	111
	USEFUL WEB SITES	116
	RECOMMENDED READING	116
	EXERCISES, PROBLEMS, AND WEBLEMS	117
1	EVOLUTION OF PROTEIN STRUCTURE AND FUNCTION	125
	Introduction	126
	Protein structure classification	126
	Secondary, tertiary, and quaternary structure	133
	Domain swapping	135
	Classifications of protein folding patterns	135
	Catalogues of protein structures	135
	Structural Classification of Proteins (SCOP)	136 138
	FSSP and the DALI domain dictionary	
	Structural relationships among homologous proteins	140
	Changes in proteins during evolution give clues to the roles of residues at different positions	142
	Evolution of the globins	. 143
	Mammalian globins	144
	The structures of globins	147
	Truncated globins	149
	Evolution of NAD-binding domains of dehydrogenases	150
	Comparison of NAD-binding domains of dehydrogenases	152
	Evolution of visual pigments and related molecules	157
	Selection and vertebrate opsins	162
	How do proteins evolve new functions?	164
	Directed evolution	169
	Classification of protein functions	170
	The Enzyme Commission (EC) classification The Gene Ontology Consortium™	173 175
		175
	USEFUL WEB SITES RECOMMENDED READING	173
	EXERCISES, PROBLEMS, AND WEBLEMS	177
5	PROTEIN ENGINEERING, FOLDING, PREDICTION, AND DESIGN	185
_	The significance of protein engineering	185
	Protein folding	186
	Thermodynamics and kinetics—key concepts	188
	Entropy	188

Spontaneity and equilibrium

189

CONTENTS

	Kinetics	190
	Thermodynamics of the protein folding transition	191
	Thermodynamics of mutated proteins	192
	The effect of denaturants on rates of folding and unfolding: chevron plots	
	•	192
	The molten globule	198
	The relationship between the structure and kinetics of folding: contact order	198
	Folding funnels	199
	Protein misfolding and the GroEL-GroES chaperone protein	200
	The GroEL-GroES conformational change	202
	Operational cycle	203
	Protein structure prediction and modelling	204
	Critical Assessment of Structure Prediction (CASP)	205
	Homology modelling	206
	Threading	207
	Prediction of novel folds	208
	Prediction of protein function	211
	Sometimes specific constellations of residues provide signature	
	patterns in the sequence that identify an active site	212
	Structural data provide additional routes to function prediction	212
	Interaction patterns, contextual information, and intergenomic comparisons are useful indicators of function	242
	Protein design	213
	-	213
	USEFUL WEB SITES	215
	RECOMMENDED READING	215
	EXERCISES, PROBLEMS, AND WEBLEM	216
6	PROTEINS WITH PARTNERS	221
	Introduction	221
	General properties of protein-protein interfaces	223
	Burial of protein surface	223
	The composition of the interface	224
	Complementarity	224
	Specific interactions at protein–protein interfaces	224
	Multisubunit proteins	226
	Protein–DNA interactions	227
	Structural themes in protein–DNA binding and sequence recognition	228
	Some protein-DNA complexes that regulate gene transcription	230
	λ cro	230
	The eukaryotic homeodomain antennapedia	232
	Leucine zippers as transcriptional regulators	233

		CONTENTS
	Zinc fingers	233
	The E. coli Met repressor	234
-	The TATA-box binding protein	234
	p53 is a tumour suppressor	235
	Virus structures	237
	Tomato bushy stunt virus (TBSV)	241
	Bacteriophage HK97: protein chain-mail	242
	The photosynthetic reaction centre	243
	Membrane transport	247
	Specificity of the potassium channel from Streptomyces	
	lividans—room to swing a cation?	247
	ATPase	248
	USEFUL WEB SITES	251
	RECOMMENDED READING	251
	EXERCISES, PROBLEMS, AND WEBLEMS	252
	ballerstay, 1 House Hay, 1110 House Hay	
7	PROTEINS IN DISEASE	255
	Introduction	256
	Diseases of protein aggregation	258
	Amyloidoses	258
	Alzheimer disease	259
	Parkinson disease	261
	Huntington disease	261
	Prion diseases—spongiform encephalopathies	261
	Serpins: SERine Protease INhibitorS—conformational disease	263
	Conformational states	263
	Mechanism of protease inhibition by serpins	266
	The immune system	266
	Antibody structure	267
	The constant, the variable, and the hypervariable	269
	The antigen-binding site	270
	Conformations of antigen-binding loops of antibodies	271
	Greater variability in the H3 loop	273
	Somatic mutation and the maturation of the antibody response	273
	Proteins of the major histocompatibility complex (MHC)	274
	Structures of MHC proteins	276
	Specificities of the MHC system	279
	Class I and class II MHC proteins function in parallel, selecting different immune	280
	responses to extracellular and intracellular pathogens	280
	Peptide binding	
	T-cell receptors	282 282
	The TCR–MHC–peptide complex	202

CONTENTS

Cancer		283
Malfunctions in two classes of genes contribute to the		. 203
development of cancer	í	284
Viruses and cancer		285
Cancer and protein structures	•	285
USEFUL WEB SITES		286
RECOMMENDED READING		286
EXERCISES, PROBLEMS, AND WEBLEMS		-
- NOBLEMS, AND WEBLEMS		288
EPILOGUE		291
ABBREVIATIONS		
GLOSSARY		293
		297
INDEX A		307