

CONTENTS

<i>List of boxes</i>	xiii	Membrane solubilization	49
<i>Preface</i>	xiv	Lipid removal	51
1 INTRODUCTION	1	Model membranes	51
General features of membranes	1	Monolayers	52
Paradigm 1: the amphiphilic molecules in membranes assemble spontaneously due to the hydrophobic effect	4	Planar bilayers	54
Paradigm 2: the Fluid Mosaic Model describes the membrane structure	5	Patch clamps	57
A shift in the paradigm: biomembranes have lateral domains that form “rafts”	9	Supported bilayers	57
A view for the future: dynamic protein complexes crowd the membrane interior and extend its borders	9	Liposomes from SUVs to GUVs	60
For further reading	13	Multilamellar vesicles	60
		Small unilamellar vesicles	61
		Large unilamellar vesicles	61
		Short-chain/long-chain unilamellar vesicles	62
		Giant unilamellar vesicles	62
		Mixed micelles and bicelles	63
		Blebs and blisters	64
		Nanodiscs	66
		Conclusion	67
		For further reading	67
2 THE DIVERSITY OF MEMBRANE LIPIDS	14	4 PROTEINS IN OR AT THE BILAYER	69
The acyl chains	14	Classes of proteins that interact with the membrane	69
Complex lipids	17	Proteins at the bilayer surface	70
Phospholipids	19	Extrinsic/peripheral membrane proteins	70
Sphingolipids	20	Amphitropic proteins	74
Sterols and linear isoprenoids	21	Lipid-anchored proteins	74
The lipid bilayer matrix	22	Reversible interactions of peripheral proteins with the lipid bilayer	77
Structure of bilayer lipids	22	Effects of peripheral protein binding on membrane lipids	77
Diffusion of bilayer lipids	24	Interactions between peripheral proteins and lipids	78
Lipid asymmetry and membrane thickness	27	Domains involved in binding the membrane	81
Lipid polymorphism	28	Curvature	83
Lamellar phase	28	Modulation of binding	84
Hexagonal phase and the amphiphile shape hypothesis	29	Proteins and peptides that insert into the membrane	85
Cubic phase	30	Toxins	86
Miscibility of bilayer lipids	31	Colicins	88
Lateral domains and lipid rafts	34	Peptides	88
Detergent-resistant membranes	35	SecA: protein acrobatics	90
Diversity of lipids	37	Proteins embedded in the membrane	91
Conclusion	39	Monotopic proteins	91
For further reading	41	Integral membrane proteins	91
		Protein–lipid interactions	97
		Hydrophobic mismatch	101
		For further reading	103
3 TOOLS FOR STUDYING MEMBRANE COMPONENTS: DETERGENTS AND MODEL SYSTEMS	42		
Detergents	43		
Types of detergents	43		
Mechanism of detergent action	46		

5 BUNDLES AND BARRELS**105****Helical bundles****105**

Bacteriorhodopsin	105
Photosynthetic reaction center	109
The proteins	110
Lipids	112
The cofactors	112
Antennae	113
The reaction cycle	114

 β -barrels**115**

Porins	117
OmpF and OmpC	118
VDAC, a mitochondrial porin	122
Specific porins	123
PhoE, the phosphoporin	123
LamB, the maltoporin	124
Other β -barrel transporters	124
Iron receptors	125
Outer membrane secretory proteins:	
not β -barrels	126

Conclusion**127****For further reading****127****6 FUNCTIONS AND FAMILIES****130****Membrane enzymes****130**

Diacylglycerol kinase	132
Presenilin, an intra-membrane protease	134
P450 cytochromes	136

Transport proteins**137**

Transport classification system	138
Superfamilies of ATPases	139
ABC transporter superfamily	140
Group translocation	140
Symporters	142
Antiporters	142
Ion channels	143

Membrane receptors**144**

Nicotinic acetylcholine receptor	144
G protein-coupled receptors	145

Bioinformatics tools for membrane protein families**146**

Predicting TM segments	146
Hydrophobicity plots	148
Orientation of membrane proteins	149
The positive-inside rule	150
Inverted repeats	151
Genomic analysis of membrane proteins	153

Helix-helix interactions**162****Proteomics of membrane proteins****163****Predicting β -barrels****164****For further reading****165****7 PROTEIN FOLDING AND BIOGENESIS****168****Protein folding****169**

Folding α -helical membrane proteins	170
bR folding studies	173
Folding studies of β -barrel membrane proteins	175
Other folding studies	177
Whole protein hydrophobicity scale	178

Biogenesis of membrane proteins**178**

Export from the cytoplasm	180
The translocon	187
The translocon structure	187
TM insertion	189
Biological hydrophobicity scale	191
Topogenesis in membrane proteins	195

Misfolding diseases**198****For further reading****201****8 DIFFRACTION AND SIMULATION****203****Back to the bilayer****203****Liquid crystallography****204**

Liquid crystal theory	206
Joint refinement of x-ray and neutron diffraction data	207

Modeling the bilayer**209**

Simulations of lipid bilayers	209
Molecular dynamics	209
Monte Carlo	213

Lipids observed in x-ray structures of membrane proteins**215****Crystallography of membrane proteins****219****A multidisciplinary approach****223****For further reading****225****9 MEMBRANE ENZYMES****226****Prostaglandin H₂ synthase****227****OMPLA****230****Membrane proteases****234**

OmpTins	234
Intramembrane proteases	235
Rhomboid protease	236
Structure of the bacterial rhomboid GlpG	237

Contents

Formate dehydrogenase	239	The vitamin B ₁₂ uptake system	310
P-type ATPases	243	BtuCD-BtuF, an ABC transport system	311
Ca ²⁺ ATPases	243	BtuB, an outer membrane transporter	
Na ⁺ , K ⁺ ATPase	250	energized by TonB	313
Other P-type ATPases	254	Drug efflux systems	316
Conclusion	255	Sav1866 and P-glycoprotein,	
For further reading	255	ABC exporters	316
		EmrE, an example of dual topology	318
		Tripartite drug efflux via a membrane vacuum	
		cleaner	320
		AcrB, a peristaltic pump	321
		Alternating site mechanism of AcrB	322
		AcrA, a periplasmic adaptor protein	323
		TolC, the channel-tunnel	323
		Partners of TolC	325
		Conclusion	325
		For further reading	326
10 MEMBRANE RECEPTORS	257		
G protein-coupled receptors	258		
Rhodopsin, a light-sensitive GPCR	259		
Ground state rhodopsin	260		
Activated rhodopsin	261		
Rhodopsin as prototype	263		
Adrenergic receptors	267		
β ₂ AR structure	268		
β ₁ AR structure	270		
Activated β ₂ AR in complex with G _s	270		
Neurotransmitter receptors	274		
Glutamate receptors: GluA2	274		
Cys-loop receptors and GluCl	278		
Conclusion	282		
For further reading	282		
11 TRANSPORTERS	284		
Secondary transporters	284		
MFS transporters	285		
LacY, a scrutinized symporter	285		
GlpT, an MFS antiporter	288		
EmrD, an MFS exporter in an occluded			
conformation	289		
FucP, an MFS symporter in			
co conformation	290		
A paradigm for MFS transporters	291		
Mitochondrial ADP/ATP carrier	291		
AAC structure	291		
Neurotransmitter transporters	294		
Glutamate transporters and GltPh	294		
Neurotransmitter sodium symporters			
and LeuT	296		
LeuT structure	298		
Transport mechanism of LeuT	300		
The NSS family and the LeuT (APC-fold)			
superfamily	300		
BetP and osmoregulated transport	303		
ABC transporters and beyond	306		
Maltose transporter	306		
		12 CHANNELS	328
		Aquaporins and glycerol aquaporins	329
		Structure of aquaporins	330
		Glycerol aquaporins: GlpF	331
		Human aquaporins: AQP4	333
		Potassium channels	335
		KcsA structure and selectivity	336
		Gating and activation	337
		Voltage gating	339
		Gating in human potassium channels	341
		Chloride channels and the CLC family	343
		CLC-ec1	344
		CLC channels as “broken transporters”	346
		Mechanosensitive ion channels	347
		MscL	349
		MscS	350
		MS channel gating	351
		Gap junction channels	354
		Conclusion	356
		For further reading	356
		13 ELECTRON TRANSPORT AND	358
		ENERGY TRANSDUCTION	
		Complexes of the respiratory chain	359
		Complex I	359
		Conformational coupling mechanism	363
		Cytochrome bc₁	365
		The Q cycle	366
		High-resolution structures	366

Cytochrome c oxidase	371	14 IN PURSUIT OF COMPLEXITY	385
High-resolution structures	371		
Oxygen reduction	373		
Proton pathways	374		
F₁F₀-ATP synthase	375	Complex formation	386
Subunit structure and function	377	Conformational changes and	
F ₁ Domain	377	dynamics	390
F ₀ Domain	379	For further reading	392
Regulation of the F ₁ F ₀ -ATPase	379	<i>Appendix I: Abbreviations</i>	393
Catalytic mechanism of a rotary motor	380	<i>Appendix II: Single-Letter Codes for Amino Acids</i>	397
Rotational catalysis	380	<i>Index</i>	399
Conclusions	383		
For further reading	383		