

Contents

Preface *xvii*

Part I Introduction *1*

I.1 Early Nerve Studies *3*

I.1.1 Galenos of Pergamon and the Animal Spirits *3*

I.1.2 Descartes and the Hydraulic Nerve *4*

I.1.3 Gassendi, Willis, and Newton *6*

I.1.4 Galvani, Volta, and the Electrical Nerve *9*

I.2 The Early Period of Electrophysiology *12*

I.2.1 Emil du Bois-Reymond *12*

I.2.2 Hermann von Helmholtz *13*

I.2.3 Julius Bernstein *14*

I.3 The Hodgkin–Huxley Model and Beyond *17*

I.3.1 The Model of Hodgkin and Huxley *17*

I.3.2 Ion Channel Proteins as Pores *20*

I.3.2.1 The Finding of Quantized Ion Currents by Neher and Sakmann *21*

I.3.2.2 Gating *23*

I.3.3 Biochemical Pathways *23*

I.4 Another Line of Thought *25*

I.4.1 Schrödinger and Physics in Biology *25*

I.4.2 Early Studies on Mechanical Stimulation *26*

I.4.2.1 The Mechanical Action Potential *28*

I.4.3 From Helmholtz to Hill: The Absence of Heat Production in Nerves *30*

I.4.3.1 Archibald V. Hill and His School *32*

I.4.4 Thermodynamic Properties of Nerves *33*

I.4.4.1 The Nerve Pulse as a Density Pulse or Soliton *34*

I.5 Scope of This Book *36*

Part II	Thermodynamics	39
II.1	Fundamental Laws in Thermodynamics	41
II.1.1	Observations	41
II.1.2	Variables	41
II.1.3	Conjugated Variables	42
II.1.4	Functions of State	42
II.1.5	The First Law of Thermodynamics	43
II.1.5.1	Work	44
II.1.5.2	Carnot Cycle	44
II.1.6	The Introduction of Entropy	46
II.1.7	The First Law and the Second Law	47
II.1.7.1	The First Law	47
II.1.7.2	The Second Law	47
II.1.8	Enthalpy and Free Energy	48
II.1.9	The Heat Capacity	49
II.1.10	Adiabatic Compression	49
II.1.11	Summary: Key Ideas of Chapter II.1	50
II.2	Some Statistical Thermodynamics	52
II.2.1	The Canonical Ensemble	52
II.2.2	The Boltzmann Distribution	53
II.2.3	Statistical Interpretation of Entropy	55
II.2.4	Thermodynamic Averaging	57
II.2.5	Microcanonical Ensemble	57
II.2.6	Summary: Key Ideas of Chapter II.2	57
II.3	Nonequilibrium	59
II.3.1	Einstein's Considerations About Boltzmann's Law	59
II.3.2	The Entropy as a Potential	60
II.3.3	The Gaussian distribution	61
II.3.4	Thermodynamic Forces and Fluxes	61
II.3.5	Onsager's Phenomenological Equations	63
II.3.6	Summary: Key Ideas of Chapter II.3	63
II.4	The Fluctuation Relations	65
II.4.1	Forces and Fluctuations	65
II.4.2	Susceptibilities	66
II.4.2.1	Heat Capacity and Enthalpy Fluctuations	66
II.4.2.2	Compressibility	67
II.4.2.2.1	Isothermal Volume Compressibility and Volume Fluctuations	67
II.4.2.2.2	Isothermal Area Compressibility and Area Fluctuations	67
II.4.2.3	Bending Elasticity and Curvature Fluctuations	67
II.4.2.4	Capacitance and Charge Fluctuations	68

II.4.3	Time Scales	69
II.4.4	Summary: Key Ideas of Chapter II.4	70
Part III Properties of Nerves 73		
III.1	Structure of Nerves	75
III.1.1	Types and Sizes of Nerves and Neurons	75
III.1.2	Myelin	76
III.1.3	Phase Transitions in Nerve Membranes	78
III.1.4	Summary: Key Ideas of Chapter III.1	79
III.2	Electrical Properties of Nerves	80
III.2.1	Voltage	80
III.2.1.1	Intracellular Recordings	80
III.2.1.2	Extracellular Recordings	81
III.2.2	Stimulation Threshold	83
III.2.3	Refractory Period	84
III.2.4	Summary: Key Ideas of Chapter III.2	86
III.3	The Dimensions of the Nerve Pulse	87
III.3.1	Velocity, Timescale, and Dimension of Action Potentials	87
III.3.2	Dependence of the Nerve Pulse Velocity on Axon Diameter	89
III.3.3	Temperature Dependence of the Conduction Velocity	90
III.3.4	The Timescale of a Nerve Pulse	91
III.3.5	The Spatial Dimensions of a Nerve Pulse	93
III.3.6	Summary: Key Ideas of Chapter III.3	94
III.4	Mechanical Properties of the Nerve Pulse	96
III.4.1	Mechanical Recordings of the Action Potential: Thickness Changes	96
III.4.2	Contraction of Nerves	98
III.4.3	Mechanical Stimulation of Nerve Pulses	100
III.4.4	Stimulation by Ultrasound	101
III.4.5	Summary: Key Ideas of Chapter III.4	103
III.5	Optical Changes During the Action Potential	104
III.5.1	Summary: Key Ideas of Chapter III.5	106
III.6	Heat Production and Temperature Changes During the Nerve Pulse	107
III.6.1	Reversible Heat Production of Nerve Pulse Propagation	107
III.6.2	Excitation of an Action Potential by Sudden Changes in Temperature	110
III.6.3	Summary: Key Ideas of Chapter III.6	111
III.7	Magnetic Fields Generated During the Action Potential	112
III.7.1	Magnetic Fields of Nerves	113
III.7.2	Summary: Key Ideas of Chapter III.7	114

III.8	Collisions of Nerve Pulses	115
III.8.1	Penetration of Action Potentials	115
III.8.2	Collision Block	118
III.8.3	Summary: Key Ideas of Chapter III.8	121
	Part IV Basic Principles of Electrophysiology	123
IV.1	Some Historical Considerations	125
IV.2	Cable Theory	127
IV.2.1	Currents in a Cylindrical Axon	127
IV.2.1.1	The Current Along the Cable	128
IV.2.2	Cable Equation	129
IV.2.3	Entrance Resistance and Conductance of a Cable	130
IV.2.4	Rall’s Model	131
IV.2.4.1	Validity of Rall’s Model for Real Nerves	133
IV.2.5	Summary: Key Ideas of Chapter IV.2	134
IV.3	Voltage Gating	136
IV.3.1	Voltage-clamp Experiments	136
IV.3.2	The Gate Model of Hodgkin and Huxley	138
IV.3.3	The Parametrization of Potassium and Sodium Conductance	140
IV.3.4	Summary: Key Ideas of Chapter IV.3	143
IV.4	The Hodgkin–Huxley Model	145
IV.4.1	The Membrane Current of a Nerve	145
IV.4.2	The Propagating Pulse	145
IV.4.2.1	The Pulse Velocity	147
IV.4.2.2	Hyperpolarization	147
IV.4.2.3	Threshold and All-or-nothing Spiking	147
IV.4.2.4	Refractory Period in the Hodgkin–Huxley Model	148
IV.4.3	Free Energy Dissipation During the Action Potential	149
IV.4.4	The Number of Parameters	151
IV.4.4.1	More Complicated Models for Human Neurons	152
IV.4.5	Summary: Key Ideas of Chapter IV.4	153
IV.5	Protein Ion Channels	154
IV.5.1	Voltage-gated Protein Channels	155
IV.5.2	Mechanosensitive Protein Channels	158
IV.5.3	Temperature-sensitive Protein Channels	159
IV.5.4	The Sensitivity of Protein Channels to the Lipid Environment	162
IV.5.5	Summary: Key Ideas of Chapter IV.5	164

Part V Properties of Artificial and Biological Membranes 167

V.1	Membrane Structure	169
V.1.1	The Membrane Bilayer	169
V.1.1.1	Early Membrane Models	169
V.1.1.2	The Fluid Mosaic Model	170
V.1.1.3	The Membrane More Realistically	171
V.1.2	Chemical Structure of Membrane Lipids	172
V.1.3	Membrane Proteins	173
V.1.4	Summary: Key Ideas of Chapter V.1	174
V.2	Membrane Melting	175
V.2.1	Change in Chain and Lattice Order Upon Heating	175
V.2.2	Single Lipids	176
V.2.2.1	Heat Capacity Profiles	176
V.2.2.2	Enthalpy and Entropy Changes	178
V.2.2.3	Calculating a Heat Capacity Profile	179
V.2.3	Lipid Mixtures	181
V.2.4	Melting of Biological Membranes	182
V.2.4.1	Lung Surfactant	182
V.2.4.2	Bacterial Membranes	183
V.2.4.3	Nerve Membranes	185
V.2.4.4	Cancer Cell Membranes	186
V.2.5	Summary: Key Ideas of Chapter V.2	187
V.3	Phase Behavior, Domains, and Rafts	189
V.3.1	The Mattress Model	189
V.3.2	Phase Diagrams	190
V.3.3	Membrane Domains	191
V.3.4	Domains in Lipid Monolayers	193
V.3.5	Nanodomains or Rafts in Biological Membranes	194
V.3.6	Summary: Key Ideas of Chapter V.3	197
V.4	Influence of Hydrostatic Pressure and Lateral Pressure	198
V.4.1	Hydrostatic Pressure Dependence of Membrane Melting	198
V.4.1.1	Pressure Dependence of Single Lipid Melting	200
V.4.1.2	Pressure Dependence of Lipid Mixtures	200
V.4.1.3	Pressure Dependence of Phase Diagrams	201
V.4.1.4	Biological Membranes	201
V.4.1.5	Volume Compressibility	203
V.4.2	Lateral Pressure and Tension	204
V.4.3	Compressibility of Monolayers	205
V.4.4	Summary: Key Ideas of Chapter V.4	206

x | Contents

V.5	Curvature	208
V.5.1	Helfrich's Description of Curvature Free Energy	208
V.5.2	The Bending Modulus and the Lateral Compressibility	209
V.5.3	Summary: Key Ideas of Chapter V.5	210
V.6	Influence of pH and Ionic Strength	212
V.6.1	pH and Salt Dependence of Single Lipid Melting	212
V.6.2	pH Dependence of Biomembrane Melting	213
V.6.3	Ionic Strength Dependence of Lipid Membrane and Biomembrane Melting	214
V.6.4	Summary: Key Ideas of Chapter V.6	214
V.7	Influence of Voltage	216
V.7.1	Voltage Dependence of Monolayers	216
V.7.2	Voltage Dependence of Bilayers	217
V.7.3	Membrane Capacitance	219
V.7.4	Electrostriction	220
V.7.5	Polarization of Membranes	222
V.7.6	Piezoelectricity and Flexoelectricity	224
V.7.6.1	Piezoelectricity	225
V.7.6.2	Flexoelectricity	226
V.7.7	Summary: Key Ideas of Chapter V.7	226
V.8	Influence of Drugs and Proteins	228
V.8.1	Dependence of Melting on Anesthetics	228
V.8.2	Dependence of Melting on Neurotransmitters	230
V.8.3	Dependence of Melting on the Presence of Peptides and Proteins	231
V.8.4	Dependence of Melting on Cholesterol	231
V.8.5	Summary: Key Ideas of Chapter V.8	232
Part VI Fluctuations and Susceptibilities		233
VI.1	Entropy and Fluctuations	235
VI.1.1	Summary: Key Ideas of Chapter VI.1	238
VI.2	Heat Capacity	239
VI.2.1	Heat Capacity at Constant Volume	239
VI.2.2	Heat Capacity at Constant Pressure	240
VI.2.3	Summary: Key Ideas of Chapter VI.2	240
VI.3	Relation Between Enthalpy, Volume, and Area Changes	241
VI.3.1	Relation Between Heat Capacity and Volume Expansion Coefficient as Measured by Densitometry	241
VI.3.2	Relation Between Heat Capacity and Volume Expansion Coefficient as Measured by Pressure Calorimetry	242

VI.3.3	Relation Between Heat Capacity and Volume Expansion Coefficient as Measured by Pressure Perturbation Calorimetry	245
VI.3.4	The Area Expansion Coefficient	247
VI.3.5	The Consequences of the Relations Between Enthalpy, Volume, and Area	247
VI.3.6	Calculating Volume, Area, and Thickness from Heat Capacity	248
VI.3.7	Summary: Key Ideas of Chapter VI.3	250
VI.4	Transitions and Elastic Constants	251
VI.4.1	Volume and Area Compressibility	251
VI.4.1.1	Adiabatic Volume and Area Compressibility	254
VI.4.2	Bending Elasticity	258
VI.4.3	Permeability	260
VI.4.4	Summary: Key Ideas of Chapter VI.4	261
VI.5	Sound Propagation	263
VI.5.1	Sound Propagation in Three Dimensions	263
VI.5.2	Sound Propagation in Two Dimensions	265
VI.5.3	Viscoelastic Coupling	267
VI.5.4	Summary: Key Ideas of Chapter VI.5	269
VI.6	Capacitance and Capacitive Susceptibility	270
VI.6.1	Capacitive Susceptibility	270
VI.6.2	The Capacitive Susceptibility	270
VI.6.3	The Fluctuation Relation of the Capacitance	273
VI.6.4	Summary: Key Ideas of Chapter VI.6	274
VI.7	Relaxation Timescales	276
VI.7.1	Theory of Relaxation Timescales Close to Equilibrium	276
VI.7.2	Simulation of Relaxation Timescales	278
VI.7.3	Measurement of Relaxation Timescales	279
VI.7.4	Influence of Drugs on Relaxation Timescales	281
VI.7.5	Phenomenological Coefficient L	282
VI.7.6	Prediction of Relaxation Timescales in a Biological System	283
VI.7.7	Summary: Key Ideas of Chapter VI.7	283
Part VII The Soliton Theory		285
VII.1	Hydrodynamics and Sound Propagation	287
VII.1.1	Hydrodynamics in the Absence of Friction	287
VII.1.1.1	Continuity Equation	287
VII.1.1.2	Hydrostatics, Dynamics, and Euler Equations	288
VII.1.1.3	Euler Equations for Compressible Fluids and Simple Acoustics	288
VII.1.1.4	Sound Propagation in One Dimension and Sound Velocity	289
VII.1.2	Hydrodynamics in the Presence of Friction	291

xii | Contents

VII.1.2.1	Viscosity	291
VII.1.3	Navier–Stokes Equations	291
VII.1.3.1	Sound Propagation in the Presence of Friction	292
VII.1.4	Summary: Key Ideas of Chapter VII.1	293
VII.2	Sound Velocity in Nerve Membranes	295
VII.2.1	The Density Dependence of Sound Velocity	295
VII.2.2	Sound Velocity in the Presence of a Coupling to the Aqueous Interface	298
VII.2.3	The Wave Equation for a Nonlinear Behavior of the Sound Velocity	298
VII.2.4	Summary: Key Ideas of Chapter VII.2	299
VII.3	The Frequency Dependence of Sound Velocity	300
VII.3.1	An Approximate Dispersion Relation	301
VII.3.2	Summary: Key Ideas of Chapter VII.3	302
VII.4	The Nerve Pulse as an Electromechanical Soliton	303
VII.4.1	The Nervous Impulse	303
VII.4.2	Soliton Propagation	304
VII.4.3	Analytical Solution	307
VII.4.4	Dendritic Trees	308
VII.4.5	The Density Dependence of the Dispersion Term	309
VII.4.6	Thickness Changes of the Membrane During the Pulse	310
VII.4.7	Heat Exchange During the Pulse	311
VII.4.8	The Energy Density of the Soliton	313
VII.4.9	Soliton Genesis	314
VII.4.10	The Stability of Nerve Solitons in the Presence of Friction	315
VII.4.11	Summary: Key Ideas of Chapter VII.4	316
VII.5	Nerve Contraction and Pulse Trains	318
VII.5.1	Nerve Contraction	318
VII.5.2	Pulse Trains	319
VII.5.2.1	Constraint of Constant Length: Pulse Trains and Refractory Period	321
VII.5.3	Thoughts About Synaptic Transmission	323
VII.5.4	Summary: Key Ideas of Chapter VII.5	324
VII.6	Excitation of Solitons	325
VII.6.1	The Free Energy of a Solitary Pulse	325
VII.6.2	The Threshold of Soliton Excitation	328
VII.6.3	The Free Energy Density of Solitary Pulses	329
VII.6.4	Summary: Key Ideas of Chapter VII.6	331
VII.7	Pulse Collisions	332
VII.7.1	Pulses Traveling in Opposite Directions	332
VII.7.2	Simulation of the Collisions of Solitons	333
VII.7.3	Summary: Key Ideas of Chapter VII.7	335

VII.8	Pulses on Monolayers	336
VII.8.1	Pressure and Voltage Pulses	337
VII.8.2	Stimulation Thresholds	339
VII.8.3	Summary: Key Ideas of Chapter VII.8	341
	Part VIII Channels	343
VIII.1	The Permeability of Lipid Membranes	345
VIII.1.1	Permeability of Membranes Close to Transitions	345
VIII.1.2	Theoretical Considerations	348
VIII.1.3	The Emergence of Lipid Ion Channels	350
VIII.1.4	Comparison of Lipid Membrane Channels and Channels from Biological Membranes	353
VIII.1.5	Summary: Key Ideas of Chapter VIII.1	357
VIII.2	Voltage-gated Lipid Channels	358
VIII.2.1	Voltage-gated Channels in BLMs	358
VIII.2.2	Voltage-gated Single Channels in Membrane Patches	359
VIII.2.3	Rectification	360
VIII.2.3.1	Theory of Rectification in Lipid Membranes	362
VIII.2.3.2	Why Do Lipid Patches Display a Net Polarization?	364
VIII.2.4	Comparison with Proteins	365
VIII.2.5	Summary: Key Ideas of Chapter VIII.2	366
VIII.3	Mechanosensitive Lipid Channels	368
VIII.3.1	Summary: Key Ideas of Chapter VIII.3	370
VIII.4	Temperature sensing	371
VIII.4.1	Summary: Key Ideas of Chapter VIII.4	373
VIII.5	The Influence of Drugs on Membrane Permeability and Lipid Ion Channels	374
VIII.5.1	Influence of Drugs on Permeability	374
VIII.5.2	Influence of Drugs on the Emergence of Channels	375
VIII.5.3	Simulation of the Effect of Anesthetics	377
VIII.5.4	Summary: Key Ideas of Chapter VIII.5	378
VIII.6	Channel Lifetimes	380
VIII.6.1	Channel Lifetimes of Lipid Membranes	380
VIII.6.2	The Control of Lifetimes by Temperature	382
VIII.6.3	The Control of Lifetimes by Voltage	382
VIII.6.4	Comparison to Lifetimes in Protein-containing Preparations	384
VIII.6.5	Summary: Key Ideas of Chapter VIII.6	385

VIII.7	Selectivity of Lipid Channels	387
VIII.7.1	Conductance of Single Lipid Membrane Pores and the Hofmeister Series	387
VIII.7.2	Summary: Key Ideas of Chapter VIII.7	388
VIII.8	Proteins as Catalysts	389
VIII.8.1	Proteins as Catalysts for Lipid Channel Formation	389
VIII.8.2	Summary: Key Ideas of Chapter VIII.8	390
Part IX Medical Consequences		393
IX.1	Anesthesia	395
IX.1.1	Introduction to Anesthesia	395
IX.1.2	The Meyer–Overton Correlation	397
IX.1.2.1	Why Is the Meyer–Overton Correlation Not Compatible with the Binding of the Drugs to a Receptor Protein?	399
IX.1.2.2	Deviations from the Meyer–Overton Correlation	401
IX.1.3	Reformulation of the Meyer–Overton Correlation	401
IX.1.4	Melting-point Depression	401
IX.1.4.1	Why Does Melting-point Depression Explain the Deviations from the Meyer–Overton Correlation?	404
IX.1.4.2	Local Anesthetics	405
IX.1.4.3	“Blocking” of Lipid Channels by Anesthetics	408
IX.1.5	Reversal of Anesthesia by Pressure and Inflammation	409
IX.1.5.1	Pressure Reversal	409
IX.1.5.2	Reversal by Inflammation	411
IX.1.6	The Influence of Anesthetics on the Nerve Excitation Threshold	412
IX.1.7	Neurotransmitters	415
IX.1.8	Summary: Key Ideas of Chapter IX.1	416
IX.2	Adaptation	418
IX.2.1	Adaptation of Lipid Membranes to Growth Temperature	418
IX.2.2	Adaptation to Hyperbaric Pressure	419
IX.2.3	Fast Adaptation by pH Changes	420
IX.2.4	Adaptation to Solvents	421
IX.2.5	Alcoholism	421
IX.2.6	Hypothermia	422
IX.2.7	Speculations on Fever	422
IX.2.8	Summary: Key Ideas of Chapter IX.2	423
IX.3	Nerve Stretching	424
IX.3.1	Introduction to Nerve Stretching	424
IX.3.2	Nerve Tension	425
IX.3.2.1	Constant Volume	425
IX.3.2.2	Constant Radius	426

IX.3.3	Changes in Melting Temperature Induced by Nerve Stretching	426
IX.3.4	The Effect of Tension on Nerve Excitability	428
IX.3.5	Examples for the Effect of Stretching	429
IX.3.6	Summary: Key Ideas of Chapter IX.3	430
IX.4	Tremor and Bipolar Disorder	431
IX.4.1	Essential Tremor	431
IX.4.2	Lithium and Bipolar Disorder	432
IX.4.2.1	Lithium and Tremor	433
IX.4.2.2	Lithium and Alcohol	433
IX.4.2.3	Depression, Body Temperature, and Lithium	433
IX.4.3	Summary: Key Ideas of Part IX.4	433
IX.5	Ultrasound Neurostimulation	435
IX.5.1	Summary: Key Ideas of Part IX.5	437
	References	439
	Epilogue	475
	Index	481

