

Contents

Preface	vii
Abbreviations	xv
1. Introduction	1
1.1 Temporal Organization	1
1.2 General Properties of Circadian Rhythms	3
1.3 Analogies with Shorter Periodicities	5
1.3.1 An Atlas of Cellular Ultradian Periodicities	5
1.3.2 The Glycolytic Oscillator	7
1.3.3 Rhythmic Flashing of Fireflies	8
2. Circadian Organization in Eukaryotic Microorganisms	12
2.1 Circadian Rhythms in Protozoa	13
2.1.1 <i>Tetrahymena</i> spp.	13
Rhythms of Cell Division	13
Physiological Rhythms Observed During the Infradian Growth Mode	16
Circadian Rhythmicity in Metabolism and Biochemistry	17
2.1.2 <i>Paramecium</i> spp.	21
2.2 Circadian Rhythms in Unicellular Algae	22
2.2.1 <i>Acetabularia</i> spp.	22
2.2.2 <i>Chlamydomonas</i> spp.	26
2.2.3 <i>Euglena</i> spp.	28
Circadian Rhythms of Cell Division	33
Circadian Rhythms of Cell Motility	33

	Rhythm of Phototaxis	33
	Dark Motility Rhythm (<i>Dunkelbeweglichkeit</i>) ..	38
	Rhythm of Cell Settling	45
	Rhythms in Photosynthetic Capacity	47
	Rhythm in Cell Shape	51
	Oscillatory Enzymatic Activities	53
2.2.4	<i>Gonyaulax</i> spp.	55
	Circadian Rhythms in Bioluminescence:	
	Physiological Characteristics	56
	Circadian Rhythms in Photosynthesis	59
2.3	Circadian Rhythms in Fungi	61
2.3.1	<i>Neurospora</i> spp.	61
	The Rhythm of Conidiation	61
	Expression in Various Strains	62
	Light Effects	64
	Temperature Effects	66
	Other Factors	67
	Rhythm of Carbon Dioxide Production	67
	Rhythm in Adenylate and Pyridine Nucleotides ..	68
	Rhythms in Nucleic Acid Metabolism	69
	Rhythms in Enzymatic Activities	69
	Rhythms in Synthesis of Heat-Shock Proteins	71
	Rhythms in Fatty Acids	71
2.3.2	<i>Saccharomyces</i> spp.	72
3.	Cell Cycle Clocks	75
3.1	Regulation of the Cell Division Cycle	78
3.1.1	Probabilistic Models	78
3.1.2	Deterministic Models	81
	Dependent Pathways	83
	Cell Sizers	90
	Autonomous Timers: Cell Cycle Clocks and	
	Oscillators	92
	Relaxation Oscillators	93
	Limit Cycle Oscillators	103
	Quantal Cell Cycles	111
3.2	Cell Division Cycles and Circadian Oscillators	119
3.2.1	Interaction of Circadian Oscillators with the	
	Cell Cycle	120
	Circadian Oscillators and the CDC in	
	Phytoplankton and Other Unicells	120
	Circadian Clock Control of the CDC in	
	<i>Euglena</i>	126
	Entrainability	130

Persistence	134
Initiation	139
Phase Shiftability	141
Singularity Point	145
Temperature Compensation	148
Circadian Rhythms of Mammalian Cell Proliferation	150
3.2.2 Ultradian, Circadian, and Infradian Interfaces	153
The Characteristics of the Oscillator	153
Insertion and Deletion of Time Segments in Cell Cycles	155
The Circadian-Infradian Rule	160
4. Experimental Approaches to Circadian Clock Mechanisms	166
4.1 Quest for an Anatomical Locus: Autonomous Oscillators in Isolated Organs, Tissues, and Cells	166
4.1.1 Circadian Pacemakers at the Organ and Tissue Levels	167
The Hypothalamus	168
Gastropod Eyes	174
The Pineal Gland	177
Pineal Biochemistry	178
Pineal Physiology and Circadian Organization ..	179
Pineal Pacemakers In Vitro	181
Other Animal Organs and Tissues	185
Plant Pulvini and Stomata	186
4.1.2 Circadian Rhythms in Isolated Cells	187
4.1.3 Subcellular Circadian Rhythmicity	190
4.2 Tracing the Entrainment Pathway for Light Signals	193
4.2.1 Nature and Localization of the Photoreceptor	193
Plant Photoreceptors	194
Photoreceptors in Animals	197
4.2.2 Coupling Links Between Receptor and Clock	198
Light-Blocking Experiments	199
Light-Mimicking Experiments	200
Entrainment Pathway for Serotonin	200
4.3 Dissection of the Clock: Perturbation by Chemicals	206
4.3.1 Nonspecific Compounds and Respiratory Inhibitors	209
Early Studies: The Chemical Shelf	209
Deuterium Oxide	210
Respiratory Inhibitors	211
Energy Charge	213

4.3.2	Inhibitors of Macromolecular Synthesis	214
	Transcription of DNA	214
	Translation and Protein Synthesis	218
	<i>Acetabularia</i>	219
	<i>Gonyaulax</i>	224
	<i>Neurospora</i>	233
	<i>Aplysia</i>	236
4.3.3	Membrane-Active Agents	239
	Alcohols	240
	Fatty Acids	243
	Ions	248
	Potassium and Other Monovalent Ions	248
	Calcium	254
	Membrane ATPases	260
	Cyclic AMP	262
4.4	Dissection of the Clock: Molecular Genetics	264
4.4.1	Isolation of Clock Mutants	265
	<i>Chlamydomonas</i>	265
	<i>Neurospora</i>	266
	<i>Drosophila</i>	268
	Circadian Clock Mutants	268
	Ultradian Clock Mutants	272
4.4.2	Recombinant DNA Studies: Cloning Clock Genes ..	275
	Isolation of a Clock Gene	275
	Restoration of Biochemical Rhythms in	
	Transgenic <i>Drosophila</i>	276
	The Product of the <i>per</i> Locus	283
	Molecular Analysis of <i>Neurospora</i> Clock	
	Genes	287
4.4.3	Alteration of Clock Properties in Biochemical	
	Mutants	288
	Respiratory and Photosensitive Pigments	290
	Cyclic AMP	291
	Fatty Acid Metabolism and Other Biosynthetic	
	Pathways	292
	Oligomycin and Cycloheximide Resistance	293
4.5	Characterizing the Coupling Pathway: Transducing	
	Mechanisms Between Clocks and Their Hands	294
4.5.1	Rhythms of Bioluminescence in <i>Gonyaulax</i>	294
4.5.2	Rhythms of Photosynthesis in <i>Gonyaulax</i>	296
5.	Biochemical and Molecular Models for Circadian	
	Clocks	298
5.1	In Vitro Molecular Models	301
5.2	Biochemical Feedback Loop and Network Models	304

5.2.1	Ultradian Metabolic Oscillators	305
	The Glycolytic Oscillator in Yeast	305
	Elements of the Oscillator	305
	Modeling Circadian Clocks with a Glycolytic- Type Oscillator	308
	The Cyclic AMP Oscillator of the Cellular Slime Mold	311
5.2.2	Cell Energy Metabolism	313
	Energy Charge	313
	The Deposition Effect and the Generation of Circadian Periods	316
	Temperature-Compensated Ultradian Clocks in Respiration	317
5.2.3	Coupled Oscillators	318
5.2.4	Periodic Enzyme Synthesis and Other Cyclic Epigenetic Events	321
	Periodic Enzyme Synthesis	322
	Self-Sustained Enzyme Oscillations	322
	Models of Microbial Enzyme Synthesis	330
	Other Cyclic Epigenetic Events	333
5.2.5	Circadian Biochemical Oscillators	334
	Cyclic AMP Models	334
	Models Based on the Mitochondrial Calcium Cycle	336
5.2.6	Infradian Metabolic Oscillators	342
	Regulation of Metabolic Pathways in Noncircadian Sporulation Rhythms	343
	Seasonal Rhythms and Photoperiodism	344
5.3	Transcriptional (Tape-Reading) Models	346
5.3.1	Specificity and Antispecificity Factors in Time Metering	348
5.3.2	The Chronon Model	348
5.3.3	Chronogenes and Cell Division Cycles	352
5.4	Membrane Models	355
5.4.1	Early Membrane Models	356
5.4.2	Coupled Translation-Membrane Model	361
5.4.3	Monovalent Ion-Mediated Translational Control Model	363
5.4.4	Other Variations on the Membrane Model Theme ..	364
5.5	Problems and Prospects	366
6.	General Considerations and Conclusions	368
6.1	Evolution of Circadian Rhythmicity	368
6.1.1	Early Selection for Biological Clocks	368

6.1.2	Ultradian Clocks: Small Steps Toward Circadian Oscillators?	370
6.2	Multiple Cellular Oscillators	372
6.2.1	Intracellular Clockshops	372
6.2.2	Intercellular Communication and Coupled Oscillators	373
6.3	The Breakdown of Temporal Organization at the Cellular Level	380
6.3.1	Dysfunction of Cellular Pacemakers in Pathology and Disease	381
	The Cardiac Pacemaker	382
	Tremor	383
	Epilepsy	383
	Aging Clocks?	384
6.3.2	Cancer: The Malignant Transformation	384
6.4	Cellular Aspects of Chronopharmacology and Chronotherapy	385
6.5	Cellular Clocks in Development and Aging	387
6.5.1	Timing of Developmental Events	387
6.5.2	Spatial and Temporal Morphogenetic Fields	391
6.5.3	Aging: Life Cycle Clocks?	392
6.6	Epilogue	394
	References	396
	Author Index	455
	Subject Index	469