

CONTENTS

Editorial Note	xv
Preface	xvii
Contributors to the Guidebook	xxi
1 Mathematical Models in Experimental and Clinical Oncology	1
1.1 Introduction	1
1.2 Oncogenesis	2
1.2.1 The single-cell multistage model of oncogenesis	2
1.2.2 Statistical kinetics of genetically determined tumours	4
1.3 Growth	5
1.3.1 Gross patterns of macroscopic growth	6
1.3.2 Tumour growth during latency	9
1.3.3 Cell population kinetics	11
1.4 Metastasis	14
1.4.1 Statistical kinetics of metastasis	14
1.4.2 Explanatory models of metastasis	16
1.5 Tumour Response to Treatment	17
1.5.1 Assessment of response in terms of growth delay	18
1.5.2 Assessment of response in terms of tumour cure	19
1.6 Prediction of Response to Therapy	21
1.6.1 Predictive models in radiotherapy	22
1.6.2 Predictive models in chemotherapy	25
1.7 General conclusions.	28
References	28
2 Quantitative Concepts in Diagnostic Radiology, Radiotherapy and Radiation Protection	33
2.1 Introduction	33
2.2 Some Basic Radiation Physics	35
2.2.1 The production of X-rays	35

2.2.2	Interactions of radiation with matter	37
2.2.2(a)	X-rays and γ -rays	37
2.2.2(b)	Particulate radiation	40
2.2.2(c)	Atomic number dependence of interaction processes	42
2.2.3	Radiation quantities and units	43
2.3	Diagnostic Radiology	43
2.3.1	The production of radiographic images	45
2.3.1(a)	Introduction	45
2.3.1(b)	Receptor systems	47
2.3.1(c)	Geometrical factors	49
2.3.1(d)	Scatter	52
2.3.1(e)	Specialized techniques	53
2.3.2	The Assessment of Image Quality	57
2.4	Radiotherapy	59
2.4.1	Introduction	59
2.4.2	General physical aspects	60
2.4.3	Treatment planning techniques	64
2.4.3(a)	External beam therapy	64
2.4.3(b)	Surface and implant therapy	67
2.5	Radiation Protection	69
2.5.1	Some basic concepts	70
2.5.2	The design of radiation facilities	72
2.5.2(a)	Introduction	72
2.5.2(b)	X-ray and γ -ray facilities	73
2.5.2(c)	Particulate radiation facilities	76
Appendix 2.A:	Radioisotope dosimetry	76
2.A.1	Radiopharmaceutical radiation dosimetry	76
2.A.2	Calculation of cumulated activity	77
2.A.3	Calculation of absorbed dose	78
References	80
General Bibliography.	83
3	Imaging	85
3.1	Introduction	85
3.1.1	What is a medical image?	85
3.1.2	Inverse problems	87
3.1.3	Processing	88
3.2	Imaging Techniques	88
3.2.1	Radiology	88
3.2.2	Computed tomography	91
3.2.3	Nuclear magnetic resonance imaging	92
3.2.4	Nuclear medicine	96

	3.2.5	Ultrasound	100
	3.2.6	Doppler ultrasonography	104
	3.2.7	Thermography and other techniques	106
3.3		General Concepts—Resolution, Sampling, Tomography	108
	3.3.1	Linearity and stationarity	108
	3.3.2	Transforms	109
	3.3.3	Sampling	112
	3.3.4	Transfer functions and resolution	113
	3.3.5	Signal to noise ratio.	116
	3.3.6	Tomography	116
3.4		Simple Image Manipulation	124
	3.4.1	Generalized spatial deconvolution	124
	3.4.2	Linear smoothing techniques	126
	3.4.3	Linear image enhancement	129
	3.4.4	Non-uniformity and spatial distortion	132
	3.4.5	Non-linear image processing.	133
	3.4.6	Maximum entropy/maximum likelihood	136
	3.4.7	Interpolation and display mappings	138
3.5		Further Image Manipulation	143
	3.5.1	Segmentation and edge detection	143
	3.5.2	Pyramids and stacks	145
	3.5.3	Pattern recognition methods.	148
	3.5.4	Texture analysis	149
	3.5.5	Handling data in 3-D	150
	3.5.6	Data compression	152
3.6		Time-series Analysis.	153
	3.6.1	Temporal deconvolution	153
	3.6.2	Principal components/Factorial analysis	155
	3.6.3	Fitting models.	158
	3.6.4	Image sequence analysis	160
3.7		Evaluation	160
	3.7.1	Evaluation of image processing methods	160
	3.7.2	Display evaluation	161
		References	167
4		Basic Quantitative Concepts of the Circulatory System	175
	4.1	Introduction	175
	4.2	Pressure	175
	4.3	Blood Flow	177
	4.3.1	Central blood volume	180
	4.4	Vascular Resistance.	181
	4.4.1	Viscosity and laminar flow	182
	4.4.2	Turbulent flow	183

	4.4.3	Parallel vascular beds	184
4.5		Volume	185
	4.5.1	Extrapolation	186
4.6		Vascular Compliance	187
	4.6.1	Elasticity	188
4.7		Mathematical Analyses of Circulatory Function	190
	4.7.1	Complex models of the circulatory system	194
		References	194
5		Mathematical Methods in Clinical Cardiology	197
	5.1	Introduction	197
	5.2	Electrocardiography	198
		5.2.1 The electrocardiogram	198
		5.2.2 Electrocardiographic lead theory	200
		5.2.3 Orthogonal lead systems	202
	5.3	ECG Analysis by Computer	204
		5.3.1 Data compression	204
		5.3.1(a) Orthogonal expansion.	204
		5.3.1(b) Linear interpolation	207
		5.3.1(c) Huffman coding	207
		5.3.2 Baseline wander	209
		5.3.3 Digital Filtering of electrocardiographic signals	210
		5.3.3(a) Classes of digital filters	212
		5.3.3(b) Examples of useful filters.	212
	5.4	Body Surface Mapping	214
		5.4.1 Lead systems	214
		5.4.2 Techniques for interpolation.	216
		5.4.2(a) Interpolation by spline functions	217
		5.4.2(b) Interpolation using Fourier series.	218
		5.4.2(c) Interpolation using Chebyshev series	218
		5.4.3 Compression of data from body surface maps.	220
		5.4.4 Methods for interpretation of surface maps	221
	5.5	The Equivalent Cardiac Generator	223
		5.5.1 Dipole theory	223
		5.5.2 Dipole controversies	223
		5.5.3 The multiple dipole model	225
		5.5.4 The multipolar expansion.	225
	5.6	The Forward and Inverse Problems in Electrocardiography	226
		5.6.1 Basic theory	226
		5.6.2 Multiple dipoles	227
		5.6.3 Multipolar components	229
		5.6.4 Epicardial mapping	230

5.7	Vector-cardiography/Polar-cardiography	232
5.7.1	Vector-cardiography	232
5.7.2	Polar-cardiography	234
5.8	Ventricular Dynamics	235
5.8.1	Angiocardiographic methods.	235
5.8.2	Computer assisted measurement of ventricular function	237
5.8.3	Echocardiographic methods	239
5.8.4	Radionuclide methods	239
5.8.5	Comparison of various methods	240
5.9	Quantitative Coronary Arteriography	240
5.9.1	Recording techniques	240
5.9.2	Parameters of interest	243
5.9.3	Clinical evaluation	244
	References	244
6	Biomechanical Analysis of the Cardiovascular System.	247
6.1	Introduction	247
6.2	Analysis of Left-Ventricular Mechanics	247
6.2.1	Introduction	247
6.2.2	Assessment of left-ventricular myocardial distensibility and contractility properties	249
6.2.3	Analysis of intracardiac flow velocity and pressure distributions	253
6.3	Analysis of Arterial Blood Flow	257
6.3.1	Derivation of aortic diastolic-systolic pressure waveforms	258
6.3.2	Analysis of arterial pulse-wave propagation; interrelationships between arterial pressure and flow-velocity waveforms	261
6.3.2(a)	Moens-Korteweg expression for pulse-wave velocity for an inviscid fluid in an elastic, cylindrical arterial tube	262
6.3.2(b)	Clinical applications	264
6.3.3	Derivation of arterial pressure and elasticity in terms of arterial dimensions and pulse-wave velocity	265
6.3.3(a)	Non-linear stress analysis of the arterial tube to derive an expression for the arterial pressure	266
6.3.3(b)	Pulse-wave velocity.	270
6.3.3(c)	Application of the pulse velocity ex-	

	pressions to evaluation of the consti- tutive parameters and arterial pres- sure	272
6.4	Analysis of Heart Valve Vibrations	275
6.4.1	Analysis of the vibration of semi-lunar valves	276
6.4.1(a)	Background	276
6.4.1(b)	One-dimensional model of diastolic valve vibration	277
6.4.1(c)	Useful diagnostic tests developed on the basis of this model	281
6.4.2	Auscultatory dynamic analysis of atrioventri- cular valves.	282
6.4.2(a)	Background	282
6.4.2(b)	Mathematical model	283
6.4.2(c)	Comments on clinical correlations	289
6.5	Concluding Remarks	290
	References	291
7	Basic Quantitative Concepts of Lung Function	295
7.1	The Physics of Gases	295
7.1.1	Volume conversions.	295
7.1.2	Pressures and fractions of gases.	296
7.1.3	Solubility	297
7.1.4	Diffusion	298
7.2	Lung Mechanics	298
7.2.1	Lung volumes.	299
7.2.2	Lung compliance.	303
7.2.3	Resistance	303
7.3	Gas Exchange.	304
7.3.1	Gas exchange in the alveoli	304
7.3.2	The alveolar gas equation.	305
7.3.3	Diffusion	307
7.3.4	Gas transport in blood.	310
7.3.5	Oxygen content	310
7.3.6	Carbon dioxide content	313
7.4	Cardiac Output and Pulmonary Blood Flow	315
7.4.1	Blood flow measured via the blood	315
7.4.2	Blood flow measured via the airways.	315
7.4.3	Pulmonary vascular resistance	318
7.5	Distribution of Ventilation and Perfusion	319
7.5.1	Nitrogen washout curve	319
7.5.2	Physiological dead space	322
7.5.3	Shunt.	323
7.5.4	Intermediate ventilation to perfusion ratios	324

7.6	Control of Ventilation	331
7.6.1	Hypoxic ventilatory response	332
7.6.2	Hypercapnic ventilatory response	332
7.6.3	Occlusion pressure	333
	Glossary of Variables and Units in Common Usage	333
	References	334
8	Mathematical Models in Clinical Inhalation Anaesthesia.	337
8.1	Introduction	337
8.2	Historical Development of Mathematical Models of Anaesthesia.	338
8.2.1	Models of inert gas uptake	338
8.2.2	Haggard's model of the uptake and distribution of diethyl ether.	339
8.2.3	Models of anaesthetic gas uptake incorporating diffusion terms	341
8.2.4	Models incorporating regional blood flow characteristics	343
8.2.5	Interaction with cardiorespiratory function.	349
8.3	A simplified model for clinical use.	352
8.4	Closed-loop Models.	360
	References	362
9	Mathematical Models in Endocrinology and Metabolism	365
9.1	Introduction	365
9.2	The Role of Mathematical Models in Endocrinology and Metabolism	366
9.2.1	Identification of system structure	366
9.2.2	Estimation of unknown internal parameters	368
9.2.3	Predictive models for patient management	369
9.2.4	Optimal control	370
9.2.5	Diagnosis	371
9.2.6	Teaching.	371
9.3	The Mathematical Basis of Models	372
9.3.1	Mathematical approximations	372
9.3.2	Levels of modelling	373
9.3.3	Empirical and theoretical models	375
9.4	General classes of mathematical representation	376
9.4.1	Lumped deterministic models	376
9.4.2	Distributed models	378
9.4.3	Stochastic models	379
9.5	Classes of Mathematical Model of Particular Relevance to Endocrinology and Metabolism	380
9.5.1	Compartmental models	380

	9.5.2	Control system models	380
	9.5.3	Non-compartmental approaches	383
9.6		Data Requirements	385
	9.6.1	Exogenous test signals	385
	9.6.2	Forms of test signal	387
9.7		Identification and Validation of Mathematical Models	389
	9.7.1	Model identification	389
	9.7.2	Model validation	392
9.8		Case Studies	394
	9.8.1	Study of bilirubin dynamics	394
	9.8.2	Short-term blood glucose regulation	401
	9.8.3	A clinical model as an aid to the manage- ment of thyroid disease	413
9.9		Summary	421
		References	421
10		The Kidney	427
	10.1	Introduction	427
	10.2	Clearance Methods	427
	10.2.1	Measurement of glomerular filtration rate (GFR)	429
	10.2.2	Single injection clearance methods	430
	10.2.3	Measurement of the renal plasma flow	435
	10.2.4	Use of clearance techniques to quantitate tubular reabsorption	435
	10.3	Determinants of Glomerular Filtration Rate	437
	10.3.1	Glomerular capillary filtration coefficient	437
	10.3.2	Net glomerular capillary ultrafiltration pressure (P_{UF})	440
	10.3.3	Sensitivity of GFR to different parameters	446
	10.3.4	Calculation of intrarenal resistances from renal haemodynamic measurements	447
	10.4	Determinants of Peritubular Capillary Reabsorption and Role of Peritubular Capillary Dynamics in Regulating Proximal Tubular Reabsorption	449
	10.5	Mechanisms of Renal Tubular Reabsorption	456
	10.5.1	Determination of L_p , σ_s , and P_s experi- mentally	459
	10.5.2	Active transport	460
	10.5.3	Methods used to determine whether transport is passive or active	461
	10.5.4	Micropuncture methods of quantifying over- all tubular reabsorption	462

10.6	Acid–base Buffers	463
10.6.1	Chemical equilibria	463
10.6.2	pH and pK	466
10.6.3	Henderson–Hasselbalch equation	466
10.6.4	Buffer curves	467
10.6.5	Isohydric principle	468
	References.	469
11	Quantitative Aspects of the Control of Body Fluid Volume	
	and Acid–Base Status in Intensive Care.	473
11.1	Determinants of the Distribution of Body Water	473
11.1.1	Introduction	473
11.1.2	Relevant thermodynamic concepts	474
11.1.3	Osmotic forces: the van’t Hoff relationship	476
11.1.4	The Gibbs–Donnan relationship	477
11.1.5	Simple estimation of body water deficit.	479
11.1.6	Equilibrium between vascular and interstitial fluid compartments	481
11.2	Clinical Acid–Base Theory	490
	References	500
	Index	503