

Table of Contents

Dedication and Acknowledgements

Abstract English

Zusammenfassung Deutsch

Preface

Table of Contents

1	On Biological Information and the Prospect of Analyzing and Creating Biological Programs	1
1	A brief history of medicine and ethics	3
1.1	Prehistoric medicine	3
1.1.1	Evidence of prehistoric diseases	3
1.1.2	Prehistoric medical treatment?	4
1.2	The beginning of history: Egypt, Mesopotamia, India and China	6
1.2.1	Egyptian medicine	6
1.2.2	Mesopotamian Medicine	7
1.2.3	Indian Medicine	7
1.2.4	Chinese Medicine	8
1.3	Greek and Roman medicine	9
1.3.1	The philosophical background	9
1.3.2	The Cult of Asclepius	10
1.3.3	Hippocrates and the Medical School of Cos	12
1.3.3.1	Empirical concepts in Hippocratic Medicine	13
1.3.3.2	Humoral pathology	13
1.3.3.3	Dietetics, medication and surgery	14
1.3.3.4	Ethical aspects	15
1.3.4	The medical schools of Alexandria	15
1.3.4.1	Herophilus	16
1.3.4.2	Erasistratus	16
1.3.5	Roman medicine	18
1.3.5.1	Dioscorides	18
1.3.5.2	Celsus	18
1.3.5.3	Galen of Pargamum	19
1.3.5.3.1	Galens impressive anatomical and physiological discoveries ...	19
1.3.5.3.2	... were accompanied by some serious errors	20
1.4	Medicine in the Middle Ages and Islamic Medicine	21
1.4.1	Byzantine medicine	21
1.4.2	Monastic medicine and Christian misericordia	21
1.4.3	Islamic medicine	23

1.4.4	From monastic medicine to scholasticism and the foundation universities	24
1.4.5	The Plague and the Middle Ages	25
1.5	Selected steps on the way from Renaissance to Modern Times	26
1.5.1	Leonardo da Vinci; Andreas Vesalius - `critical´ anatomical observation	27
1.5.2	Paracelsus – alchemy and chemistry	28
1.5.3	Ambroise Paré - surgery	29
1.5.4	Fracastoro and Fernel – contagious diseases	29
1.5.5	The `Baconian method´ and the `scientific method´	30
1.5.6	William Harvey – blood circulation	30
1.5.7	van Leeuwenhoek - microscopy	31
1.5.8	Sydenham – a new therapeutic approach `proven´ by observation	31
1.5.9	Morgagni – pathology of solid organs	32
1.5.10	Developments in physiology and chemistry	32
1.5.11	Boerhaave – bedside teaching and a new clinical medicine	33
1.5.12	Physical examination: Auenbrugger - percussion and Laënnec – auscultation with a stethoscope	33
1.5.13	The influence of the ideas of the Age of Enlightenment	34
1.5.14	James Lind – the first clinical trial (scurvy)	34
1.5.15	Louis and medical statistics: the end of blood-letting	35
1.5.16	The foundation of scientific journals	36
1.5.17	The influence of natural sciences on medicine and developments in physiology and medical chemistry	36
1.5.18	A new era of medical pharmacology	37
1.5.19	The cell theory	38
1.5.20	Rudolf Virchow – cellular pathology	38
1.5.21	Pasteur and Koch - Bacteriology	39
1.5.22	Ehrlich, Langley and Clark – the seminal receptor concept	41
1.5.23	Salvarsan, sulfonamide and penicillin antibiotics	42
1.5.24	The rise of surgery	43
1.5.25	Semmelweis – childbed fever	43
1.5.26	Asepsis and antisepsis	44
1.5.27	Anesthesia	44
1.5.28	Surgery from the 19th to the 21st century	45
1.5.29	Clinical schools, hospitals, specialisation, nursing and other `new´ medical professions, new treatment methods, laboratory and preventive medicine, and public health	46
1.5.30	The increasing influence of technical devices and apparatus in medicine	47
1.5.31	Genetics, molecular biology and recombinant DNA science: from Mendel's laws of inheritance to Watson & Crick's DNA double helix model and beyond	48
1.6	The history of medical ethics. The central role of ethics in medicine. Historic concepts and failures	51
1.6.1	Hippocratic ethics	51
1.6.2	Ethics and religion	52
1.6.3	Influence of the ideas of Enlightenment on ethics	52
1.6.4	Nazi atrocities, the formulation of the `Nuremberg Code´ and the `Declaration of Helsinki´	53
1.6.5	The Tuskegee study	54

2	Reflections on current and future medicine and ethics	55
2.1	Modern medical ethics	55
2.1.1	Ethics committees and clinical studies	55
2.1.2	Ethical guidelines for medical practice	55
2.1.3	Utilitarianism, Kant and casuistry as underlying theories for solving ethical dilemmas	56
2.1.4	Recent and future developments in medical ethics and the paramount importance of ethics in medicine	57
2.2	Modern medicine – the status quo	61
2.2.1	The molecules and ‘molecular machines’ of life	61
2.2.1.1	DNA – a ‘molecule of life’ with information-storage capacity	61
2.2.1.2	Most molecular machines are made up of proteins	62
	The chemical diversity of the 20 amino acids provides the basis for the functional diversity of proteins	63
2.2.1.3	Some molecular machines are made up of nucleic acids	64
2.2.1.4	Lipids, carbohydrates, ions and even gases are further examples of ‘molecules of life’	66
2.2.2	Modern medicine: turning the focus of interest from organs to cells to ‘molecules of life’ and their interplay	67
2.2.3	Homeostatic regulatory circuits demonstrate that ‘molecules of life’ can convey information	68
	Insulin signaling as an example of a biological ‘regulatory circuit’	69
2.2.4	The fact that ‘molecules of life’ in ‘biological circuits’ transport information can be exploited for therapeutic purposes	70
2.2.5	Drug development is based on the receptor concept	71
2.2.5.1	Traditional drug development involves screening myriads of chemical compounds for desired effects	74
2.2.5.2	‘Rational drug design’ involves designing new drugs based on the structure of the receptor whose function is to be blocked or activated	75
	‘Rational drug design’ helped develop modern HIV and influenza drugs	77
2.2.6	Modern ‘evidence based’ medicine relies strongly on testing hypothesis by means of sound statistical studies	81
2.2.7	Identification of well-established risk factors for e.g. cardiovascular diseases has laid the basis for modern preventive medicine	81
2.2.8	Symptomatic and causal therapy	82
2.2.9	The reductionist approach versus a more ‘holistic’ approach	83
2.3	Personal reflections: two suggestions for future developments in medicine	83

3	Information, microchips and biological nanomachines - an introduction to information theory and the theory of molecular machines	85
3.1	Biological circuits can process information much like electronic circuits	85
3.2	Nanotechnology	87
3.3	Biological molecular machines and biological nano-chips	90
3.3.1	Some remarks with regard to the physical laws that govern the function of molecular machines	90
3.3.1.1	The important role of probabilities in nanotechnology and molecular biology	91
3.3.1.2	How to create reliable circuits from unreliable components	92
3.4	The close relationship between nanotechnology and molecular biology: What biologists can learn from engineers and vice versa	95
3.5	An introduction to information theory and the theory of molecular machines	96
3.5.1	Thermodynamics	96
3.5.1.1	Systems and surroundings	97
3.5.1.2	Energy, work and heat:	97
3.5.1.3	The first law of thermodynamics	98
3.5.1.4	Enthalpy	98
3.5.1.5	Entropy and the second law of thermodynamics	99
3.5.1.6	The third law of thermodynamics	101
3.5.1.7	The Clausius inequality	101
3.5.1.8	Focusing on the system: Helmholtz and Gibbs energies:	102
3.5.1.9	Gibbs free energy and the thermodynamic equilibrium constant	103
3.5.2	What is information? An introduction to information theory	104
3.5.2.1	Shannon entropy	104
3.5.2.2	Information is a reduction of uncertainty at a receiver	104
3.5.2.3	Relationship between Shannon entropy and thermodynamic entropy	105
3.5.3	Theory of molecular machines – applying information theory to biology	106
3.5.3.1	Minimum energy dissipation for a molecular machine to gain R bits of information	106
3.5.3.1.1	Molecular machines gain information while going from an ‘activated’ before state to a lower-energy after state	107
3.5.3.2	Modeling a molecular machine with a number of harmonic oscillators	108
3.5.3.2.1	The energies of such harmonic oscillators in a thermal bath obey a Boltzmann distribution, the normalized velocity components obey a Gaussian distribution	108
3.5.3.2.2	Depicting the velocity distributions of molecular machines as spheres in high dimensional Y Space	109
3.5.3.3	Shannon's Channel Capacity theorem and the Channel Capacity of Molecular Machines	110
3.5.3.3.1	The technical Channel Capacity Theorem and Codes used in technical Signal Transmission	111
3.5.3.3.2	The Channel Capacity of biological Molecular Machines and Codes used in Biology	114

4	Biophysical considerations on information in machines and in living beings	115
4.1	Information processing machines	115
4.2	Information and life	118
4.3	Various biophysical ways how information can be `represented´ are adopted for information storage, transport, and processing	121
4.4	Mass and structure are well suited for information storage	122
4.4.1	The mass and structure approach to represent and store information has accompanied mankind throughout history	122
4.4.1.1	Fingers, pebbles and coins for counting	122
4.4.1.2	Abacus, cuneiform script and seal rings	123
4.4.1.3	The advantages of using mass or structure for information storage	124
4.4.1.4	Mass and structure are less well suited for information transport and processing	125
4.4.2	Electronics: The use of structure for information storage in optical storage media and PLAs	126
4.4.3	Mass and structure for information storage in biology	128
4.4.3.1	DNA as a paradigm for information storage by means of chemical structure	128
4.4.3.2	Prostaglandins, steroid hormones and growth factors also demonstrate how chemical structure is used to represent information	134
4.4.3.3	Phosphorylation frequently represents information	144
4.5	Waves and currents transport energy and information	148
4.5.1	Electromagnetic waves and electric currents: information transport in electrical engineering and electronics	148
4.5.1.1	Maxwell's equations and the theory of electromagnetism	149
4.5.1.2	Codes for data transmission	155
4.5.2	Waves, electric and particle currents, diffusion and advection – information transport in biology	155
4.5.2.1	Vision and hearing – electromagnetic and mechanical waves	155
4.5.2.2	Diffusion, advection & ion flux in a field and oscillations & reaction-diffusion equations	164
4.6	Information processing typically involves fields – the most versatile way to `represent´ information	169
4.6.1	Signal processing in electronics: semiconductors, pn-junction, and transistors	171
4.6.1.1	Basic physics of semiconductors	171
4.6.1.2	Doping creates n-type and p-type semiconductors	174
4.6.1.3	The p-n junction	174
4.6.1.4	Transistors – the building blocks of electronic devices	175

4.6.2	Signal processing in biology – voltage gated channels, protein conformational switches, and transcription factors	178
4.6.2.1	Ion Channels of Excitable Membranes	178
4.6.2.2	Conformational `switches`, phosphorylation, transmembrane receptors and intracellular signaling molecules	188
4.6.2.3	DNA-binding proteins process information at the DNA level Sequence logos and sequence walkers	200 207
5	Assembling an information processing system from its parts	216
5.1	The Turing Machine - a mathematical model of an information processing system	216
5.2	Electronic information processing systems: The von Neumann Architecture	220
5.3	Biological information processing systems: Characteristic features of a `biological architecture`	225
	What are the prototypical components of a biological information processing unit (BIPU)?	225
5.4	A comparison of the components of electronic and biological information processing systems	232
5.4.1	Biological and electronic `logical` and `arithmetic` units	232
5.4.1.1	Boolean logic and electronic logic gates	234
5.4.1.2	Biological logic gates and multivalued (`fuzzy`) logic	242
5.4.1.2.1	BIPUs at the cell membrane	242
5.4.1.2.2	RNAi and proteins assembling on DNA can act as BIPUs	249
5.4.1.2.3	Signaling molecules as BIPUs	259
5.4.1.2.4	From enzyme kinetics to multivalued (fuzzy) logic – potential applications to biological modeling	277
5.4.1.2.5	The necessity of statistical models	284
5.4.2	Memory in electronics and in biology	285
5.4.2.1	Long-term memory	285
5.4.2.1.1	ROM, EPROM, EEPROM ...	285
5.4.2.1.2	and their biological counterparts	287
5.4.2.2	Short-term memory	295
5.4.2.2.1	SRAM and DRAM ...	295
5.4.2.2.2	... and their biological counterparts	299
5.4.3	I/O modules, protein interaction domains, and data transport	306
5.4.4	Electronic and biological `clocks`	309
5.4.5	Other types of `chips`	313
5.4.6	Overview - table	315

6	Analyzing biological programs	317
6.1	‘Reading’ and understanding biological programs	317
6.2	Challenges in analyzing biological programs	323
6.3	The ‘language’ of biological programs	326
6.4	Some methods for establishing models of biological systems	331
6.4.1	Motivation for creating quantitative models of biological systems	331
6.4.2	Chemical reaction rates and enzyme kinetics	336
6.4.2.1	Chemical equations, stoichiometry, reaction rates and Arrhenius equation	336
6.4.2.2	Collision theory	338
6.4.2.3	Diffusion-limited reactions	339
6.4.2.4	Activated complex theory	340
6.4.2.5	Potential energy surfaces	341
6.4.2.6	Enzyme kinetics, Michaelis-Menten formula, competitive and non-competitive inhibition	343
6.4.2.7	The Hill equation	344
6.4.2.8	The allosteric models of Koshland-Nemethy-Filter and Monod-Wyman-Changeux	345
6.4.2.9	The influence of external forces applied on a complex on the dissociation rate	347
6.4.3	Metabolic Control Analysis	348
6.4.4	Differential equations and nonlinear systems	356
6.4.4.1	Nonlinear systems and biological models	359
6.4.4.2	Some simple examples of differential equations for modeling biological processes	361
6.4.4.3	Phase plane analysis and bifurcation diagrams	364
6.4.4.4	The Chen model of cell cycle control in budding yeast - equations, parameters, conditions, pathway diagram and outputs of numerical solutions	369
6.4.4.5	A few notions on nonlinear dynamics and chaotic systems	378
6.4.5	Stochastic modeling and Monte Carlo simulations	382
6.4.6	Pathway diagrams	388
6.5	Experimental data for theoretical models in systems biology	400
6.5.1	In silico “experiments” and the requirement of high-throughput techniques in systems biology	401
6.5.2	RNA expression analysis with DNA microchips	402
6.5.3	Oligonucleotide hybridization and synthesis-based DNA sequencing methods	403
6.5.4	Determining the methylation status and other epigenetic information	404
6.5.5	Mass spectrometry for proteomics	406
	Isotope labeling	407
6.5.6	Genetic techniques to determine the ‘interactome’	408

7	How to `write´ biological programs	409
7.1	Biological `programs´ “run” on biological `circuits´	409
7.2	Quasi self-assembly of a biological “circuit” inside a living cell (“in vivo”)	410
7.3	Biological circuits can also be assembled “artificially” in vitro	411
7.4	A simple example of a task that a “biological program” could perform	412
7.4.1	Recognition of a particular cell surface as a form of cell-specific therapy	412
7.4.2	A few examples of effector pathways of a biological “program”	413
7.4.3	Successful repair will require a thorough understanding of biological programs	414
7.4.4	Naturally occurring vs. entirely artificially designed biological programs	415
7.5	On `finite state machines´ and the `execution´ of biological programs	415
7.6	Biological `clocks´ coordinate the “execution” of biological programs	418
7.7	Biological `subprograms´ could be “called” much like computer “subroutines” 420	
7.8	Designing new programs and new molecules	420
7.9	A few theoretical suggestions on biological programs that could possibly be built	422
7.9.1	The Repressilator	423
7.9.2	A more complex system of three mutually inhibitory genes	425
7.9.2.1	Additional regulatory binding sites for activator A and inhibitor I molecules	427
7.9.2.2	Master regulators to switch the entire circuit on and off, or to “call” biological “subprograms“	428
7.9.2.3	Input from external signals	429
7.9.2.4	How to start the “biological program” in a predetermined way	429
7.9.2.5	A biological system that stops after the first `cycle´ for a biological program that is not repeated ad infinitum	431
7.9.2.6	Different wiring diagrams and circuit designs may establish biological programs that “behave“ in a similar way	433
7.9.2.7	A logical operation on two or more different input signals	435
7.9.2.8	A potential application: How to guess which intracellular `programs´ a (cancer) cell “runs” from its outside surface	436
7.9.2.9	“Intelligent“, self-learning programs	437
7.9.2.10	Effector programs triggered in response to the results of a biological “computation”	438
7.9.2.11	Potential applications	441
7.9.2.12	Building preTELEs i.e. therapeutic biological programs	441

7.10	Theoretical model of a biological “circuit” that bears a potential for clinical application	446
7.10.1	The ‘wiring diagram’	447
7.10.2	Description of the molecules and their interactions	448
7.10.3	A stochastic model of the proposed ‘biological circuit’ and ‘biological program’	451
7.10.3.1	The molecules of the stochastic model, and the function of the entire circuit or program	453
7.10.3.2	Plots illustrating the time evolution of the biological system	456
7.10.3.3	Time evolution of the biological system for prolonged periods	463
8	Clinical applications	468
8.1	Two scenarios centered on ‘biological programs’ with considerable clinical relevance	468
8.1.1	The ‘molecular network approach’ to understanding health and disease – significance for investigating the pathophysiology of diseases, and for new diagnostic and therapeutic strategies.	469
	Molecular network-based diagnosis and ‘combination’ treatment e.g. in cancer	470
8.1.2	‘Biological programs’ and designed ‘preTELS’ (‘programmed responsive therapeutic element’) as novel therapeutic strategies	477
8.1.2.1	The rules that regulate the changes of biological ‘states’ can be regarded as biological ‘programs’	477
8.1.2.2	‘Single step algorithms’: mere blocking or activation of receptors ‘Non-conditional single step algorithms’ (acting on all receptors in the organism) versus more flexible ‘conditional single step algorithms’ (acting on a certain type of receptor only)	479 480
8.1.2.3	The limitations of single-step algorithms	481
8.1.2.4	The advantages of ‘complex algorithms’: A whole ‘biological program’ designed to operate as a ‘preTEL’ (‘programmed responsive therapeutic element’)	483
8.1.2.5	How to create ‘programs’ for therapeutic goals	484
8.1.2.6	Programmed therapies and the advantage of viewing medicine and biology as informational sciences	486
8.2	Pathology, (patho-)physiology and research on the mechanisms of disease	488
8.3	Clinical diagnosis	489
8.4	Development of ‘classical therapies’ based on a recognition of important cellular ‘disease’ programs	496
8.5	Development of ‘biological programs’ (preTELS) as a new form of medical therapy	503
8.6	Ethical considerations	513

Bibliography