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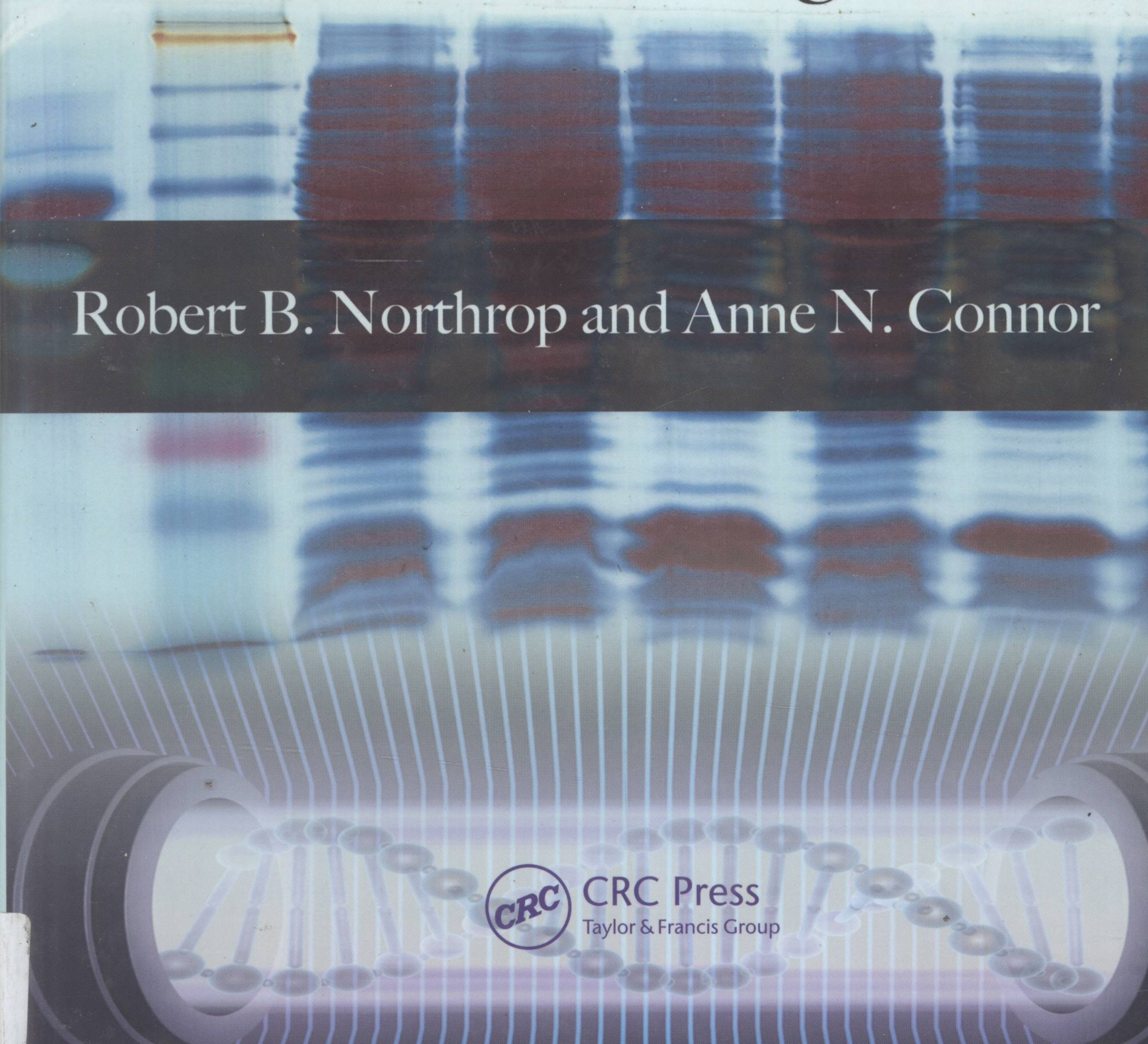
Introduction to Molecular Biology, Genomics and Proteomics for Biomedical Engineers



Robert B. Northrop and Anne N. Connor

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Dedication

We dedicate this text to our spouses, Adelaide and Michael.

Preface

This introductory textbook is intended for use in a one-semester classroom course that has the purpose of acquainting biomedical engineers and interested scientists with molecular biology. Biomedical engineers in particular will find it valuable. It has been written to provide an introduction to the broad and complex fields of molecular biology, genomics, and proteomics for engineers and scientists who have not formally studied these disciplines, and who are working with, or planning to work with, living systems. It assumes that such readers already have had courses found in engineering curricula on college algebra, basic calculus, ordinary differential equations, and perhaps linear algebra.

Efficient extraction of information from this text and the understanding of its material also requires that the reader has had introductory college courses in chemistry, cell biology, or human physiology and anatomy, and is thus familiar with what is meant by such basic terms as amino acid, cell, cell membrane, chromosome, DNA, egg, gene, germ cell, meiosis, mitochondria, mitosis, nucleus, nucleolus, protein, ribosome, RNA, sperm, zygote, etc. This textbook elaborates on the molecular biological basis for these terms and illustrates man's progress in manipulating the genome at a molecular level. Knowledge of genomics and molecular biology will also shed light on evolutionary theories and future trends in genetic medicine and stem cell research. The reader will come to appreciate the incredible complexity of the biochemical systems required to sustain life in its many forms.

RATIONALE

It may be argued that the 20th century was the age of electronics. However, the 21st century has emerged as the age of molecular biology. Researchers have identified and manipulated the structures of, and reactions between, numerous biomolecules. Their motivation has been driven largely by the search for cures for diseases and medical conditions, and to allow us to feed the world's ever-growing human population. Molecular biology is a very different discipline from the "hard sciences" of physics and chemistry and certain engineering specialties, in that it is multidisciplinary, involving not only physics, chemistry, mathematics, and engineering, but a plethora of information about hundreds of thousands of protein molecules, nucleic acids, genes, and the regulatory mechanisms making cellular biochemical reaction pathways stable, and life possible. Molecular biologists must embrace complexity.

Engineers and scientists in the 21st century very often find themselves working on the interdisciplinary interface between living and inanimate systems. Whether their work involves modeling global warming, developing new medical imaging systems, devising instruments to sense tumors early in their growth, inventing new ways to introduce manmade genetic material into cells, or designing new systems to quickly identify bacterial and viral pathogens, it is important that engineers and scientists not initially trained in molecular biology, biochemistry, genomics, and proteomics have a working background in these areas to be able to communicate effectively and work with bioscientists.

For example, engineers trained in systems analysis and mathematical modeling have cooperated with molecular biologists to model the dynamics of biochemical pathways. However, this type of interdisciplinary interface is not without turbulence. Clearly, the more biology and biochemistry the engineers know, and the more mathematics the cell biologists know, the better will be their communication and the more fruitful their endeavors.

The very complex biochemical relations that permit life to exist are described and illustrated in this text. It is largely about the specialized organic molecules in living organisms and how they interact and react. However, it is a primer, not intended as an academic shortcut or a replacement for formal, in-depth course work in biochemistry, molecular biology, genomics, and cell biology. It is intended to broaden the background and pique the interest of undergraduate students in all branches of engineering; in particular, biomedical, electrical, and chemical engineers, some of whom may choose to enter the field of genetic engineering or become involved in the design of analytical instruments for use in molecular biology, genomics, proteomics, and even ecological systems. It will also help students in chemical engineering, electrical and computer engineering, and biomedical engineering appreciate the instrumental methods used to diagnose genetically based diseases.

The reader will gain knowledge about the awesomely complex chemistry of life and how it may be modeled and manipulated in genomic-based medicine and genetic engineering. Controversial topics such as stem cell research, cloning, parthenogenesis, and chimeras are described, and ethical problems in molecular biology are covered.

DESCRIPTION OF THE CHAPTERS

In Chapter 1, Introduction, key terms in biology are defined and discussed. Also considered are the properties of linear, nonlinear, and complex nonlinear systems and the challenge of modeling them. Living systems and biochemical systems in living organisms are seen to use feedback to effect self-regulation (homeostasis), and the dominant feedback mechanism in molecular biological systems is observed to be parametric control.

In Chapter 2, Life and Death, definitions and properties of life are considered. An overview of the domains and kingdoms used to classify living organisms is given. Viruses are considered to be nonliving, self-replicating genomic "machines." Also covered are theories for the origin of life on Earth. Cell death is described; the molecular biological systems for apoptosis and necroptosis are outlined. Death in metazoans (including human brain death) is viewed from the point of the failure of critical (modular) organ-systems.

In Chapter 3, Review of Basic Cell Anatomy and Physiology, we consider the cell as the basic unit of life. The distinction between Prokaryotes (bacteria) and Eukaryotes (single-celled, metazoan and plants) is presented. Subsystems in eukaryotic cells are described (structure and function), including cell membranes, transmembrane proteins and their various roles, the cytosol, and the roles of the diverse intracellular components of eukaryotes (e.g., nucleus, nucleolus, ribosomes, endoplasmic reticulum, Golgi apparatus, lysozomes peroxisomes, mitochondria, etc.). Also covered are the process of cell division and the cell cycle. The differences and similarities between mitosis and meiosis are described. Finally, intercellular signaling by changes in transmembrane potential are covered.

In Chapter 4, Introduction to Physical Biochemistry and Biochemical Systems Modeling, we review the basic physical chemistry of biochemical reactions. Types of chemical bonds, the role of catalysts and enzymes, and chemical kinetics based on mass action are described. Two ubiquitous, coupled reactions (glycolysis and the citric acid cycle) and their stoichiometry and energy balances are described in detail, followed by a section detailing other metabolic pathways (for carbohydrates, lipids, and amino acids). Photosynthesis is described. Finally, the challenge of modeling biochemical system dynamics is treated, and a number of software programs that can be used in quantitative molecular biology are listed.

In Chapter 5, The Basis of Genetic Inheritance, classical Mendelian inheritance is described. Exceptions to Mendel's rules, epigenetic inheritance, and genetic imprinting are introduced. The role of a cell's genome is presented, including exons and introns, and the enigma of the sequential biochemical regulation of development (gene expression, protein synthesis) is reviewed. The genetic code and the central dogma of protein synthesis (the codon, transcription, and translation) are treated in detail.

In Chapter 6, Nucleic Acids and Their Functions, the roles of DNA and RNA in a cell's command, control, and communication (C^3) structure are given. The many types of RNAs used by a cell, together with their functions, are also covered. DNA repair mechanisms, and gene regulation are introduced.

In Chapter 7, A Review of Proteins, proteins are the tail that wags the molecular biological dog. Whereas there are about 23,000 human genes, there may be over 230,000 proteins possible from the human genome. This large chapter begins with a description of the 20 AAs and the peptide linkages used to form the primary (linear) structure of proteins. How proteins achieve their tertiary structures is discussed, along with the role of chaperone proteins. Numerous examples of protein functions are given, ranging from structural applications and hormones to ion pumps. The misfolded prion protein, the cause of "mad cow disease," is examined in detail as an example of the consequences of an acquired error in protein structure. Finally, we describe the processes of protein destruction and AA recycling, including the role of the proteosome.

In Chapter 8, The Genetic Basis for Certain Inheritable Diseases: Genomic Medicine, the linkages between certain diseases and defects in certain genes are described. The list is large and growing yearly. We see that many diseases are only correlated with gene defects, others are caused by them. This chapter also introduces gene therapy where genetically modified (GM) viruses have been used experimentally to fight certain cancers.

In Chapter 9, Some Instrumental Methods Used in Genomics, Proteomics, and Forensic Science, we describe some of the physical techniques used to characterize and measure nucleic acids and proteins. The polymerase chain reaction (PCR), rolling circle amplification (RCA), and padlock probes are described as means of amplifying and characterizing DNA and RNA oligos. The use of fluorescent molecular tags is described. How DNA is manipulated in forensic science is clearly presented. Section 9.7 details a number of techniques used to characterize large protein molecules, including the use of microarrays, ELISA tests, and x-ray crystallography.

In Chapter 10, Applications of Genomics, we describe the controversial introduction of genetically modified organisms (GMOs) into the human and farm animal food chain. Examples of GMOs are given, illustrating their pros and cons. Recombinant DNA technology is described, including the physical means by which new genetic material is introduced into plants and animals. This chapter also explains animal reproductive cloning. The sources of stem cells, and how they can benefit regenerative medicine, is treated in detail. There is also a unique section on the role of cancer stem cells in the propagation of tumors. The controversial topics of parthenogenesis and chimeras are also described.

In Chapter 11, Ethical Issues in Genetic Engineering, we consider the trichotomy between short-term financial profits aiding humanity by producing more (GM) food and the potential harm that can befall the ecosystems where certain GM foods are grown and also the consumers of GM foods. Also considered are the ethical problems caused by harvesting embryonic stem cells from IVF embryos and the creation of animal chimeras.

FEATURES

Some of the unique features of this text are:

- The first three chapters review basic biology and cell biology; the components of prokaryotic and eukaryotic cells are described. The origin of life and the significance of cellular and organismic death are considered.
- Chapter 4 introduces the reader to physical molecular biology, including types of biochemical bonds, reaction energetics, catalysts, and enzymes. Mass-action kinetics are introduced and used to model biochemical oscillators ("clocks") and the generation of the nerve action potential. For those interested in quantitative biology, there is an extensive listing of available biochemical systems simulation software.

- Chapter 7 covers the ubiquitous roles of *proteins* in all life processes and underscores their importance in all living systems, as well as in viruses.
- Chapter 8, on genetic diseases, introduces the role of our genomes and epigenomes in determining our health.
- Chapter 9 describes in detail many of the important instrumental techniques used in characterizing and quantifying nucleic acids, proteins, and other biomolecules.
- Chapter 10 describes the role of stem cells in regenerative medicine, their future potential in effecting cures, and the sources of stem cells. The control of stem cell differentiation is seen to be a major problem.
- Chapter 10 also has a unique section (10.4.5) on the role of adult stem cells in the growth and metastasis of cancer.
- Chapter 11 treats ethical concerns inherent in the production of GMOs and in the harvesting of embryonic stem cells.

This text has a large, comprehensive glossary with detailed definitions to aid the nonbiologist in accumulating the vocabulary of the biological sciences. The bibliography and references will aid the reader in pursuing topics in detail. (Entries are from textbooks, current journal articles, and, of course, the Internet.) Over 30 color diagrams aid in the interpretation of molecular structures and biochemical reactions.

Robert B. Northrop
Chaplin, Connecticut

Anne N. Connor
San Antonio, Texas

Authors

Robert B. Northrop, Ph.D. majored in electrical engineering at Massachusetts Institute of Technology (MIT), graduating with a bachelor's degree in 1956. At the University of Connecticut (UCONN), he held a graduate assistantship while he studied for a master's degree in systems engineering, which he earned in 1958. In 1958, as the result of a long-standing interest in living systems, he entered the Ph.D. program there in physiology as a research fellow in cell biology. He did research on the neuromuscular physiology of molluscan catch muscles and earned his Ph.D. in 1964.

In 1963, Northrop rejoined the electrical engineering department of UCONN as a lecturer and was appointed assistant professor in 1964. In collaboration with his Ph.D. advisor, Dr. Edward G. Boettiger, he secured a 5-year training grant in 1965 from the National Institute of General Medical Science (NIGMS) of the National Institutes of Health (NIH) and started one of the first interdisciplinary biomedical engineering graduate training programs in New England. UCONN currently awards M.S. and Ph.D. degrees in this field of study and has a robust undergraduate specialization in biomedical engineering, based in the Electrical and Computer Engineering Department.

Throughout his career, Dr. Northrop's areas of research have been broad and interdisciplinary and centered on biomedical engineering. He has conducted sponsored research on the neurophysiology of insect and frog vision and devised theoretical models for visual neural signal processing. He also conducted sponsored research on electrofishing, and he developed, in collaboration with Northeast Utilities Service Co., effective working systems for fish guidance and control in hydroelectric plant waterways on the Connecticut River using underwater electric fields.

Another area of Dr. Northrop's sponsored research has been in the design and simulation of nonlinear, adaptive, digital controllers to regulate in vivo drug concentrations or physiological parameters, such as pain, blood pressure, and blood glucose in diabetics. An outgrowth of this research led to his development of mathematical models for the dynamics of the human immune system that were used to investigate theoretical therapies for autoimmune diseases, cancer, and HIV infection.

Biomedical instrumentation has also been an active research area: An NIH grant supported studies on the use of the ocular pulse to detect obstructions in carotid arteries. Minute pulsations of the cornea from arterial circulation in the eyeball were sensed using a no-touch, phase-locked, ultrasound technique. Ocular pulse waveforms were shown to be related to cerebral blood flow in rabbits and humans.

Recently, he addressed the problem of noninvasive blood glucose measurement for diabetics. Starting with a Phase I SBIR grant, Dr. Northrop developed a means of estimating blood glucose by reflecting a beam of polarized light off the front surface of the lens of the eye and measuring the very small optical rotation resulting from glucose in the aqueous humor, which, in turn, is proportional to blood glucose. As an offshoot of the instrumental techniques developed in micropolarimetry, he developed a magnetic sample chamber for glucose measurement in biotechnology applications. The water solvent was used as the Faraday optical medium. His current research interest lies in complex systems.

Dr. Northrop has written seven textbooks, with topics including analog electronic circuits, instrumentation and measurements, physiological control systems, neural modeling, signals and systems analysis in biomedical engineering, instrumentation and measurements in noninvasive medical diagnosis, and analysis and application of analog electronic circuits in biomedical instrumentation.

Dr. Northrop was on the electrical and systems engineering faculty at UCONN until his retirement in June 1997. Throughout this time, he was director of the biomedical engineering graduate program. As emeritus professor, he still teaches courses in biomedical engineering, writes texts, sails, and travels. He lives in Chaplin, Connecticut, with his wife.

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Anne N. Connor, M.A. is a writer, researcher, and analyst for Methodist Healthcare Ministries, a medical nonprofit organization in San Antonio, Texas. Her educational background includes a bachelor's degree from Dartmouth College, where she was a teaching assistant in the English Department. She received honor citations in chemistry and sociology. Her master's degree in communications is from the University of New Mexico at Albuquerque. She considers herself an autodidact and has immersed herself heavily in the field of genomics for the past 4 years. She is a graduate of the Leadership Texas Class of 2006 and has received numerous awards for her work, most recently a humanitarian award from the health care community in San Antonio. She is a member of Phi Beta Kappa, Phi Kappa Phi, and the writers' organization Gemini Ink.

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