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978-0-521-87070-2 - Chemical Biophysics: Quantitative Analysis of Cellular Systems
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Introduction

Nearly every area of modern research in biology and biomedical science is targeted in one way or another on gaining quantitative understanding of the behavior of biochemical systems. Cellular metabolic pathways, genetic regulatory systems, and protein interaction networks represent different examples of biochemical systems that obey a common set of physicochemical laws, and may be analyzed and simulated based on a common set of principles derived from such laws. It is the purpose of this book to introduce and make use of the methods for the analysis and simulation of biochemical systems that lie at the foundation of current and future research in biological and biomedical science.

Computational biology

Since the time of Newton, a key scientific strategy has been to understand physical systems based on their representation in terms of the smallest possible subsystem (i.e., model) that captures the important mechanistic interactions. The influence of gravity in maintaining the earth's orbit about the sun is satisfactorily explained by analyzing the equations of motion representing a universe consisting of two massive bodies; a complete mathematical analysis of the three-body problem remains out of reach. Living biological systems consist of not two, or even two hundred interacting components. Analysis, prediction, and rational manipulation of cellular function requires a mechanistic understanding of physical systems of unimaginable complexity. Thus the computer is an essential tool in helping us to analyze and simulate living systems.

The term *computational biology* has emerged to describe theoretical and computer-aided analysis and prediction of biological behaviors.[1] Yet while the

[1] Unfortunately the vocabulary of biology is often imprecise. The terms *computational biology* and *bioinformatics* are interchangeable in some circles. Here we define computational biology as specifically focusing on the use of

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terminology may be new, the practice of computational biology is not [15]. In 1919 August Krogh and Agner Erlang established one of the first mathematical models of a living system [118], used to predict the oxygen distribution around a capillary based on a model formulation that is still in use today [136, 157]. It has been over five decades since Alan Hodgkin and Andrew Huxley published their work using computational modeling to characterize the electrophysiological function of the squid giant axon [94, 95, 96, 97, 98]. Current work in computational biology takes advantage of computational resources that are well beyond anything that was available to Krogh or Hodgkin and Huxley. Yet in terms of clarity, precision, and insight, the work of these Nobel Prize winning physiologists continues to set the standard for the field. The Krogh–Erlang model is analyzed in Chapter 8 of this text; the Hodgkin–Huxley model in Chapter 7.

Systems biology

Systems biology – another recently emerged term – is widely used to define the current era of biomedical research. While no simple universal definition of systems biology exists, in vague terms systems biology is the application of a systems view to biology research. Since biological systems are complex collections of interacting parts, the aim is to study the operation of the system as a whole rather than that of the individual parts in isolation. Thus computational biology is an essential component of systems biology. In fact, we can enumerate a number of specific roles that computational biology plays in (systems) biology research.

(i) To analyze data. Computational models are used to translate measured data that provide indirect measurements on the function of biological systems into quantitative mechanistic information.
(ii) To formulate hypotheses. Hypotheses that are quantitative and subject to quantitative testing are best formulated as computational models. A computational model of a biological system represents a precise unambiguous hypothesis regarding the operation of that system.
(iii) To fix/improve hypotheses. Given a disproved or inadequate specific hypothesis, computational models will suggest possible improvements to the hypothesis to explain the available data.[2]
(iv) To generate further hypotheses. Given validated and verified models (i.e., hypotheses) of subcomponents of a system, these models may be integrated together to predict behavior of the integrated system and generate predictions to be tested.

mathematical and computational tools to simulate and analyze the biophysical processes underlying biological phenomena, and bioinformatics as focusing on managing and mining large-scale data that emerge from high-throughput biotechnologies. The former is the subject of this book.

[2] Often we cycle between items (ii) and (iii) in this list as our understanding becomes more sophisticated and our models become less wrong. This idea is outlined elegantly in Platt's essay on *Strong Inference* [158].

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(v) To design optimal experiments. A computational model provides a means of designing experiments for which the hypotheses to be tested (see item (ii) in this list) are sensitive to the variables to be measured.

(vi) To transfer information obtained from one experimental regime to apply to another. For example, the potential impact of observations on enzyme expression levels on metabolic function can be explored using a computational model of the given enzymes and related biochemical pathways.

The key to being able to do all of the above is to be able to build physically realistic models of biological systems. Since basic physical principles circumscribe the behavior of biological systems, we place a special emphasis on physical realism in computational biology and simulation of biochemical systems in this text. Models developed this way attain certain *a priori* validity that is missing in models based on experimental data alone. Viewed from this perspective there is nothing fundamentally novel in the systems biology endeavor. In his Nobel lecture Eduard Buchner argued in 1907 that "the differences between the vitalistic view and the enzyme theory have been reconciled" [25]. By building biological theory on a foundation of physicochemical theory, we will ensure that vitalism does not creep back into the study of biology in the twenty-first century. As Buchner put it, "We are seeing the cells of plants and animals more and more clearly as chemical factories, where the various products are manufactured in separate workshops." This way of seeing cells (and organs and organisms) is at the philosophical foundation of this text.

Inherent in the study of biological systems is the notion of *emergent properties* – the idea that the functions of a complex system transcend the properties of all its individual parts. It is fair to say that the most rigorously understood emergent properties in nature are related to how the observed macroscopic properties of matter arise from the microscopic behavior of atoms and molecules. This is the domain of statistical thermodynamics. Thus the analysis of biochemical systems in terms of statistical thermodynamics provides a natural framework within which current applications in systems biology from electrical, chemical, and computer engineering (such as feedback in networks, optimization, statistical inference, and data mining) may be integrated into a consistent theory of biological systems [78]. One goal of this text is to build a bridge between physical chemical concepts and engineering-based analysis of biological systems.

Organization of this book

This book is organized into three parts. The first part introduces background material on physical chemistry and the treatment of kinetics and thermodynamics in biochemical reactions. While the concepts introduced in Chapter 1, *Concepts from*

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physical chemistry, are essential for assimilating material in the remainder of the text, detailed mathematical derivations related to this material are not essential and appear in Chapter 12. Key concepts that directly relate to material in the later chapters are introduced and/or reviewed. The second chapter of Part I, *Conventions and calculations for biochemical systems*, introduces the concepts of apparent equilibrium constants and apparent Gibbs free energy, and shows how these concepts are applied to in vivo and in vitro biochemical systems. The third chapter covers basic techniques in modeling and simulating chemical systems.

Part II of this book represents the bulk of the material on the analysis and modeling of biochemical systems. Concepts covered include biochemical reaction kinetics and kinetics of enzyme-mediated reactions; simulation and analysis of biochemical systems including non-equilibrium open systems, metabolic networks, and phosphorylation cascades; transport processes including membrane transport; and electrophysiological systems. Part III covers the specialized topics of spatially distributed transport modeling and blood–tissue solute exchange, constraint-based analysis of large-scale biochemical networks, protein–protein interactions, and stochastic systems.

Since the scope of this book is broad, one could write a whole book on the topics of several of the chapters herein. Indeed for many topics, such books exist. Therefore throughout this book, typically at the conclusion of a given chapter, we refer the reader to a number of excellent texts that we have found useful in studying and synthesizing the important concepts in the analysis of biochemical systems.

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Part I

Background material

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1

Concepts from physical chemistry

Overview

An essential property of all living systems is that they operate in states of flux, transporting and transforming mass, transducing free energy between chemical, electrical, and mechanical forms, and delivering signals and information in terms of biochemical activities. Consequently, the principles governing the behavior of biochemical systems are the principles of physical chemistry. As an introduction to background material necessary for describing and understanding the behavior of biochemical systems, this chapter covers the concepts of chemical thermodynamics including temperature, entropy, chemical potential, free energy, and Boltzmann statistics.

In the early nineteenth century Carnot gave birth to the field that came to be known as thermodynamics, with the first theoretical treatise on mechanical work and efficiency in heat engines [28]. Over the course of that century, a complete physical theory of how changes in heat, mechanical work, and internal energy of molecular systems are related – in short the theory of thermodynamics – was assembled by Clausius, Helmholtz, Boltzmann, Gibbs, and others. As part of the thermodynamic theory a number of familiar physical quantities were introduced, including entropy, enthalpy, and free energy. We shall see that understanding these quantities and how they are related is essential for building physically realistic simulations of biochemical systems.

1.1 Macroscopic thermodynamics

Our study begins with an enumeration of the laws of thermodynamics:

0. If two systems have the same temperature as a third, then they have the same temperature as one another.
1. The total energy of an isolated system is conserved.

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2. The entropy of an isolated system does not decrease.
3. The minimal entropy of a system is achieved at the temperature of absolute zero.

Readers may recall encountering these famous laws (expressed in either this form or related equivalent forms) in a number of places – from chemistry to engineering courses – during their student careers. Yet it is our experience that knowledge of these laws does not necessarily translate into proficient understanding and application. The disconnect between knowledge and understanding may arise from the fact that while the laws are simple and straightforward, the quantities that they govern may be somewhat mysterious. For example, the so-called zeroth law makes a precise statement about the physical quantity temperature. Yet the quantity temperature is not defined, leaving us without an understanding of the physical significance of the statement.

Of the three quantities (temperature, energy, and entropy) that appear in the laws of thermodynamics, it seems on the surface that only energy has a clear definition, which arises from mechanics. In our study of thermodynamics a number of additional quantities will be introduced. Some of these quantities (for example, pressure, volume, and mass) may be defined from a non-statistical (non-thermodynamic) perspective. Others (for example Gibbs free energy and chemical potential) will require invoking a statistical view of matter, in terms of atoms and molecules, to define them. Our goals here are to see clearly how all of these quantities are defined thermodynamically and to make use of relationships between these quantities in understanding how biochemical systems behave.

To illustrate the potential disconnect between knowledge and understanding in the study of thermodynamics, consider the basic equation of macroscopic thermodynamics [88],

$$dE = TdS - PdV + \mu dN, \tag{1.1}$$

which relates infinitesimal changes in internal energy E, entropy S, volume V, and number of particles N in a system, to the temperature T, pressure P, and chemical potential μ. Armed with Equation (1.1) and the second law of thermodynamics, which we will encounter in several different forms throughout this book, one may develop all of the relevant formulas of macroscopic thermodynamics. For example, if the volume and number of particles in a system is held constant then the following relationship is apparent:

$$\left(\frac{\partial S}{\partial E}\right)_{N,V} = \frac{1}{T}. \tag{1.2}$$

In Equation (1.2) we have used the conventional notation $(\cdot)_{N,V}$ to specify that the expression in parentheses is computed holding N and V constant.

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The definition of the Gibbs free energy $G = E - TS + PV$ may be combined with Equation (1.1) to show the following.

$$\begin{aligned} dG &= dE - TdS - SdT + PdV + VdP \\ dG &= \mu dN - SdT + VdP \\ \left(\frac{\partial G}{\partial N}\right)_{T,P} &= \mu. \end{aligned} \tag{1.3}$$

Yet mathematical manipulations such as above do not tell us why it is useful to introduce G as a thermodynamic variable. We shall see in Section 1.4.1 that systems held at constant temperature and pressure – i.e., typical laboratory conditions and a reasonable approximation for most biological systems – spontaneously move in the direction of lower G. Therefore gradients in Gibbs free energy represent the thermodynamic driving force for constant temperature and pressure (isothermal and isobaric) systems. To appreciate why this is the case, we need first to develop some ideas about how large numbers of microscopic particles interact and exchange energy under different macroscopically imposed conditions.

In the following sections we will see how temperature, entropy, and free energy are statistical properties that emerge in systems composed of large numbers of particles. In Chapter 12, the appendix to this book, we dig more deeply into statistical thermodynamics, derive a set of statistical laws that are used in this chapter, and show how Equation (1.1) – the fundamental equation of macroscopic thermodynamics – is in fact a statistical consequence of more fundamental principles operating at the microscopic level.

1.2 Isolated systems and the Boltzmann definition of entropy

An isolated system is defined to be a system that does not exchange material or energy with its environment. Thus the extensive thermodynamic variables N, V, and E are held fixed. Boltzmann's formula for the entropy of such a system is

$$S = k_B \ln \Omega(N, V, E), \tag{1.4}$$

where k_B is the Boltzmann constant, and $\Omega(N, V, E)$ is the total number of *microstates* that are available to the system at given values of N, V, and E. (The term *microstate* refers to the microscopic configuration of the system. For classical systems the microstate is defined by the positions and momenta of all particles making up the systems. For quantum mechanical systems the number $\Omega(N, V, E)$ can be obtained by counting the number of independent solutions to the Schrödinger equation that the system can adopt for a given eigenvalue E of the Hamiltonian [156].)

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Similarly, if one is interested in a macroscopic thermodynamic state (i.e., a subset of microstates that corresponds to a macroscopically observable system with fixed mass, volume, and energy), then the corresponding entropy for the thermodynamic state is computed from the number of microstates compatible with the particular macrostate. All of the basic formulae of macroscopic thermodynamics can be obtained from Boltzmann's definition of entropy and a few basic postulates regarding the statistical behavior of ensembles of large numbers of particles. Most notably for our purposes, it is postulated that the probability of a thermodynamic state of a closed isolated system is proportional to Ω, the number of associated microstates. As a consequence, closed isolated systems move naturally from thermodynamic states of lower Ω to higher Ω. In fact for systems composed of many particles, the likelihood of Ω ever decreasing with time is vanishingly small and the second law of thermodynamics is immediately apparent.

Combining Equations (1.1) and (1.4), we can develop a statistical interpretation of the thermodynamic quantity temperature,

$$\left(\frac{\partial S}{\partial E}\right)_{N,V} = k_B \left(\frac{\partial \ln \Omega}{\partial E}\right)_{N,V} = \frac{1}{T}, \tag{1.5}$$

which states that temperature is a measure of the relationship between number of microstates and the internal energy of matter.

1.3 Closed isothermal systems

1.3.1 Helmholtz free energy

In biology and chemistry we are usually not interested in the study of isolated systems. Biological systems exchange energy and material with the environment and it is important to understand what are the thermodynamic driving forces in such systems. Since biochemical processes occur in an aqueous environment, we wish to treat the environment in a rigorous way without worrying about the details of the solvent molecules' conformations and interactions. The statistical thermodynamic approach to this problem was introduced by Josiah Gibbs [49].

In this section we study closed systems (closed to mass transport but not energy transfer) held at constant temperature. In statistical mechanics these systems are referred to as NVT systems (because the thermodynamic variables N, V, and T are held fixed). We shall see that the Helmholtz free energy represents the driving force for NVT systems. Just as an isolated system (an NVE system) evolves to increase its entropy, an NVT system evolves to decrease its Helmholtz free energy.

Since a system of constant volume and mass held at constant temperature exchanges energy with its surroundings, we can no longer define a fixed total internal

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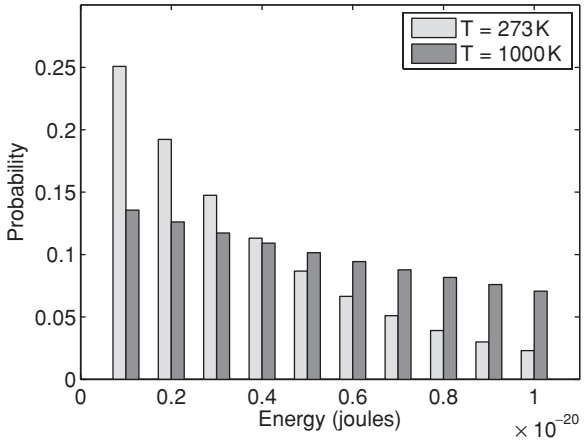

Figure 1.1 Illustration of the Boltzmann probability law of Equations (1.6) and (1.7). The state probability distribution is plotted at two different temperatures for a system with ten possible microstates with energy ranging from 10^{-21} to 10^{-20} joules. At the lower temperature ($T = 273$ K), the lower-energy states are significantly more probable than the higher-energy states. At the higher temperature ($T = 1000$ K), the energy distribution becomes more uniform than at the lower temperature.

energy E of the system. The probability of a microstate that has internal energy E is proportional to $e^{-E/k_B T}$, according to the Boltzmann probability law. (See Section 12.2.) Thus the probability of a state can be calculated

$$P(E) = \frac{e^{-\beta E}}{Q}, \tag{1.6}$$

where

$$Q = \sum_i e^{-\beta E_i}, \tag{1.7}$$

where the factor β is equal to $1/k_B T$. The summation in Equation (1.7) is over all possible states i. The Boltzmann probability law is illustrated in Figure 1.1. Using this probability law, we can determine an expression for the *average* internal energy U. In general, with the NVT probability distribution function defined according to Equation (1.6), we can calculate the expected value of a property of the system as

$$\langle f \rangle = \frac{\sum_i f_i e^{-\beta E_i}}{Q} \tag{1.8}$$

where $\langle f \rangle$ is the expected value of some observable property f, and f_i is the value of f corresponding to the ith state. The average internal energy of a closed isothermal

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