Chapter 2
Philosophy and Practice of Biophysical Study

Contents

2.1 What Is Biophysical Chemistry and Why Study It?

As a field, biophysical chemistry is an interdisciplinary area of study in which biological systems are regarded with the somewhat quantitative and concrete eye of the physical scientist. In using the intellectual paradigm of biophysical chemistry, we attempt to understand a biological phenomenon by carefully describing the essentials of its physical nature. This gives us the advantage of using the tools of the physical scientist to explore the complexities of biological systems. These tools are essentially the language and formalisms of mathematics, physics,

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and chemistry. The underlying philosophical foundation of biophysical chemistry is that application of the principles of these fields to biological systems will lead to meaningful and useful knowledge. Although it is impossible to advance understanding of biological problems using a biophysical paradigm without being knowledgeable about the underlying physical and chemical principles, when teaching and presenting these fundamentals, both the instructor and the student tend to get lost in the physical details and forget the overall purpose for the investigation. In this volume we will endeavor to find the proper balance.

Recently a newer term, *molecular biophysics* is often found alongside the more traditional name, biophysical chemistry. Is there a difference between these two topics? In this text, we will recognize the distinction but regard them as not being very different. In practice (such as the naming of courses of study at a University), these two topics are often differentiated but from our philosophical worldview, it is far more cogent to view them as the same. Operationally they might be differentiated by the property that biophysical chemistry is “intellectually” willing to embrace topics at the phenomenological level and proceed with physical analysis even when a molecular basis and understanding is not yet known. Molecular biophysics takes as its starting point that some knowledge of the molecule is given and then applies physical analysis. Sometimes in biophysical chemistry, progress is made and the behavior of the system under study is elucidated even when molecular detail is unavailable. There is the expectation this approach will then lead to a more detailed molecular-explanation level for the phenomenon in due course. The biophysical chemist will therefore be able to measure and quantitatively model complex phenomena such as the nerve action potential or protein folding in physical terms before understanding the physical structure of the molecules that give rise to the behavior. The molecular biophysicist would be more inclined to focus first on a detailed description and understanding of the molecule before attempting to understand its integration and response to its physical environment. The researcher whose efforts use physical methods such as x-ray crystallography or NMR spectroscopy to define the structure of a macromolecule such as a sodium channel would be inclined to identify oneself as a molecular biophysicist (or structural biologist). Alternatively, the scientist seeking the relationship of how mechanical traction alters the electrical conductivity of a lipid membrane in aqueous electrolyte solution of NaCl might call oneself a biophysical chemist. We will take the position that these are two ends of the same field of inquiry – both cases of the application of the fundamental study of physics, which is the search for the fundamental set of rules and actors in such a fashion that general principles can be inferred that are explanatory and predictive when applied to often dizzyingly complex and diverse biological systems. We will generally refer to the overall field as biophysical chemistry but will use the terms interchangeably guided by the context – always recognizing that the underlying scientific viewpoint is the same.

2.2 Science Is Not Content but a Unique Method of Discovery

Biophysical chemistry is a branch of *modern scientific inquiry* that uses a physical perspective in its application of the scientific method. What we mean by the *scientific method* needs precise definition because it differentiates modern science from other methods of exploration and explanation. Science is defined as a human endeavor that explores the natural world. By no means is science the only method for exploring the natural world but it *is* distinct from other means. What makes modern scientific inquiry distinct is an insistence for *validation* of observations and relationships with a *skeptical empiricism* that requires both rational, *logical reasoning* and *evidence* that is generated by carefully done *experimentation*. Content information (often casually called "the science" by both lay and scientific workers) is often considered to be the essence of a scientific discipline. This is an error. Content information is not science but is the product of scientific inquiry and its methods properly applied. Ideally content information that is discovered and validated by the methods of science should be identified with the adjective "scientific." This specifically tags the subsequent information as resulting from an operation of scientific inquiry: the scientific method that has been applied to an object or event of interest. The process of scientific inquiry always starts with observations of some aspect of the natural world. The first step of scientific observation is characterized by systematically organizing these analyses into a description of the system being observed. This systematic organization characterizes each *modern*, *proto*-, and *Aristotelian* scientific inquiry. We will name this overall group *holo-scientific* in our following discussions. Because biophysical chemistry is a product of modern scientific inquiry, when the unmodified term is used, the reader should assume reference is being made to *modern* scientific inquiry.

It is useful in holo-scientific analysis to take the view that everything can be treated as a "system." A system is described using the following definitions:

- A *system* is a set of elements (e.g., parts, events, components, objects both physical and metaphorical) that are connected and that form a complex whole.
- The *properties* of systems are typically emergent from the overall operation of the system.
- *Observables* are properties that are measurable.
- A *description of a system* includes a notation of its
  - *Elements*,
  - *Relationship rules* defining how the elements interact,
  - *Context or background space* in which the elements and rules are found and operate,
  - *State*, which is defined by a set of observable properties that are measured together. *Patterns* of observables are typically used to define the state of a system. The identification of these patterns to define the "state" of biological systems is the focus of the field of "systems biology,"
  - *Equations of state* that define how the observables are related,
  - Typically the elements comprising a system are themselves further describable as systems (i.e., they are *subsystems)*. System properties are usually distinct from the individual characteristics (or properties) of the subsystem components of the system.

2.3 The Progression of Inquiry Guides the Scientific Modeling Process

Models are partial descriptions (or abstractions) of systems of interest. A "good" model is an abstraction at an appropriate level of detail that "accurately" represents the reality of the system of interest. Staged model making is the central process of the method of modern science. The practice of a cycle of critical analysis, hypothesis creation and skeptical empiricism to confirm hypotheses, and observation is named "*the progression of inquiry*." Thus a description of the dynamic of modern science is based on three linked stages of model making. These are the following:

- Formation of *descriptive models* that represent observations (of systems of interest).
- Generation of *explanatory models* that embed hypothetical linkages of causality (relating how the system of interest works).
- Creation of *experimental models* that allow empirical testing of the hypothesized relationships of the explanatory and the epistemological nature of the descriptive models. This empirical testing validates or falsifies the models by comparison of predictions derived from theory (hypotheses) to the measured experimental data.

Many models employ the abstraction that the system under study is static or unchanging over time. Many systems are, in fact, unchanging or static in the time frame of interest so this can be an important and reasonable abstraction. However this abstraction is unreasonable when some aspect of the system as described above changes with time. When changes in system elements, rules of interaction, context, emergent properties, states, or equations of state over time are required for accurate description and explanation of a system under study, dynamic modeling is required. Dynamic modeling explicitly follows changes in the system over time and in many cases a single timescale is inadequate to the task. If necessary, multiple timescales must be incorporated in the model. The mathematical tractability of such models is inversely proportional to the dynamical complexity. Sometimes the dynamical model can be shown to arrive at a dynamic equilibrium and can thus be treated as if it were a static model unchanging over time.

At this point it is adequate to understand that the process of modeling identifies and abstracts certain system-descriptive details of a real system under study and maps them to a formal system that is the model. It is correct to conceptualize the process of modeling as an *operator* thus indicating a *mathematical operation* on a real system to produce the formal model. When we wish to invoke a systems modeling operation that transforms an observation into a description of system as given above it can be designated it with the operator symbol Υ. We write the modeling operator:

$$\Upsilon(x) \tag{2.1}$$

This says find the "system of x." Thus, if we wish to describe the phenomenon of muscular action (which we will do later in the chapter) we could write this as $\Upsilon(\text{action}_{\text{muscle}})$. In Chapter 4 we will extend our treatment of model making and its discipline, systems science.

With the operation of making a systems description defined we can further recognize that the progression of inquiry or scientific method is also an operator, ΠE. The transformation of a descriptive model (which is the output of $\Upsilon(x)$) into an experimentally validated causal model is an iterative process that is supervised by the progression of inquiry and can be written as

$$\Pi E\,[\Upsilon(x)] \tag{2.2}$$

Thus we define the scientific method as a paradigm for inquiring into the natural world such that

(1) observations (x) are organized using systems analysis into descriptive models, $\Upsilon(x)$;
(2) testable hypotheses that may be either correlational or causal in nature are proposed as connecting the elements and relational rules that characterize the descriptive models. This leads the transform of the descriptive model into an explanatory model of linked hypotheses (a theoretical model);
(3) predictions of values expected to be taken by a dependent variable when an independent variable is set, result from phrasing the hypotheses as relationships linking these variables;
(4) a scientific experiment which is a formal mapping of the theoretical model is done in which only the independent variable(s) is altered. The design of the scientific experimental model is a large part of the day-to-day practice of scientific investigation;
(5) experimental evidence supporting validation of the tested hypothesis is established when the value of the predicted observable is consistent with measured experimental value.

The terminology, experimental methodologies, theoretical approaches, and history of a scientific discipline may vary between fields but this fundamental process of discovery and validation is a general and shared operation.

2.4 A Brief History of Human Methods of Inquiry Reveals Important Aspects of the Scientific Method

Arguably the scientific method (modern science) is one of the most successful discoveries in over 300,000 years of human endeavor. In the half millennium since its development and application, human civilization has seen an overwhelming evidence of the power of modern science (the process) and of scientific knowledge to alter and mostly improve the human condition. Advancing knowledge of the natural world in which we live (the prime objective of holo-scientific study) continues on an exponential rise because of the modern method. How did this remarkable process of progress come to pass? Since the whole of science is a human endeavor that explores the natural world, it is the human brain with its strengths and weaknesses that does the exploring. A sense of our modern view of science can be gained by following a brief history of holo-scientific thought.

All (holo) science starts with observations of the patterns of the natural world. Archeological evidence from cave paintings and the notching of bone and reindeer horns suggests that pre-historic humans were extremely careful in their recording of seasonal and temporal patterns. Such knowledge is acquired by simple observation. A hunter/gather society depends on this level of inquiry to know where and when animals gather, feed, obtain water, or sleep; to know when and where berries, shrubs, and flowers are located that will bear fruit; and to know the patterns of weather, drought, and flood so that migration ensures the survival of the society. An agricultural society also depends on this basic knowledge to know when to plant, when to reap, and when to gather and store food.

However, observation alone is not "modern" science; simple observation leads to "proto-science." Proto-science accepts observations without question or verification. The human brain always tries to organize observations of its world into unambiguous models of cause and effect. This does not mean that the models are correct, only unambiguous. Models of cause and effect are built on a mode of explanation or a context. A mode of explanation establishes the way that cause-and-effect relationships explain the natural world. Historically, humans and their cultures have used several modes of explanation in their attempt to formulate the cause-and-effect models that give meaning to their observations of the natural world. Three important modes of explanation seen in the history of humans are as follows:

- Received knowledge
- Ways of knowing
- Modern skeptical-empiricism

Received knowledge. This mode of explanation attributes the cause for events to Gods, magic, and mystical powers. It leads to mythological and theological explanations for the events discovered in the natural world. Mystical attribution is usually based on "received knowledge" or knowledge that is passed "down" invariably by those who have previously "received these truths." The observed evidence, which may be quite accurate and detailed, is interpreted in a God–demon–magic context. For much of human history, patterns of importance to hunter-gatherer and agricultural civilizations have been used to ensure survival of the society. For most of human experience, the causality relations were attributed to supernatural Gods and magical occurrences. Thus, a "proto-science" based on observation with theological attribution has existed for most of humankind's history.

Ways of knowing. The ancient Greeks made extremely careful observations about their natural world. They developed models that explained the observations according to strictly rational, logical deductions. The starting point for these deduced models was derived from “self-evident” truths. These models of thought assumed that the actions of the Universe were rational, according to a human-rationalized order. In the Greek (Aristotelian) view, the philosophical mind saw truth and perfection in the mind and imposed it onto the Universe. For example, the Greek view on motion might follow this narrative:

- The Gods who made the world are perfect.
- Circles and straight lines are perfect.
- Gods make motion.
- Motion must be perfect because the Gods made it.
- Therefore, motion in the natural world is circles and straight lines.
- By corollary, planets (where Gods live and which must therefore be perfect) move in circles and cannon balls move in straight lines.

The problem with “ways-of-knowing” models of explanation is that all observations are forced to fit the model. The underlying model cannot be changed by evidence. This mode of explanation is resistant to any change in the worldview because new observations cannot alter the underlying models of cause and effect. For example, the idea that motion occurred in straight lines led medieval military engineers to calculate that a cannon ball would rise to a certain height and then fall straight down over a castle wall. However, the cannon balls did not land according to the medieval engineers’ expectations. The Aristotelian “way of knowing” was not able to provide a means to correct the error between what was expected and what happened.

Both of the “received knowledge” and “ways of knowing” modes of explanation satisfy the brain’s goals of completing patterns of cause and effect and of avoiding ambiguity. However, the particular viewpoint of these modes of explanation enhances the brain’s intrinsic tendency to lock onto pre-set biases. Neither the “received knowledge” nor the “ways of knowing” modes of explanation has the capacity to alter the underlying worldview. These modes of explanation are, therefore, limited in their flexibility and capacity to expand their field of knowledge beyond a relatively restricted plane of observation. Both are like looking at the world through a fixed focus lens or, in the most extreme case, closing the lens completely and considering only what is already known and accepted as the extent of relevant knowledge.

Modern skeptical-empirical science. During the Italian Renaissance, Leonardo da Vinci (1452–1519), who was a very good military engineer, tried to solve the problem of the “mortar shells that kept missing.” da Vinci’s approach was radical for his time. He observed that when a mortar was fired, the shell followed a path that was not the one predicted by “perfect” motion. There was no straight-line motion at all! Instead the shell followed the path of a “parabola.” He changed his world’s view based on his experiments and measurements. da Vinci’s mortars began to hit their targets, and the seeds of modern experimental science were planted. The growth of these seeds occurred subsequently in the work of Galileo (1564–1642) and Kepler (1571–1630), whose story we will touch on in the next section.

In the scientific mode of explanation, the fundamental rules are discovered not from assumption or philosophical musing, but rather from careful consideration, measurement, experiment, and analysis of specific, relatively simple cases. Observation is the first step in constructing a model, then testable hypotheses are proposed for relationships within the model. The validity of the model and its hypotheses is tested by making a prediction, performing experiments to test the prediction, making experimental measurements, recognizing that the observer may influence the experiment, accounting for that influence (design of controls) and, then, changing (discarding or revising) the model when the experimental evidence requires a different worldview.

Instead of using a strictly deductive logic that dictated reality from a series of "self-evident" propositions, modern science began by breaking from this tradition and using inductive logic. In the framework of deductive logic, the general proposition exists first. The specific case is logically found starting with the general case and working toward the specific one. In inductive logic, the principles of rational order still stand, but the first step is the consideration of specific cases that are carefully studied, and then the specific case is generalized backward to fundamental principles. In a system of inductive logic, the fundamental rules are usually discovered not from progressing from assumptions, but rather through the questioning of assumptions following measurement, experiment, and analysis.

Modern science uses experimental models and inductive logic to balance the internal formal explanatory models that human imagination formulates. This is an important interaction in modern science. Here we do a brief experiment to explore this balance between a vital human mental capacity and the exploration of the natural world:

2.5 The Gedanken Experiment Is a Thought Experiment

Imagine yourself standing outside a country home on an early spring morning just before sunrise. Take a deep breath and shiver to the taste of the sweet pre-dawn air. Listen carefully to hear the chirping of morning birds. As the sun reaches the horizon, glinting shafts of light reach your eyes. Another deep breath and you feel a peace that comes from a resonance between you and the world at your doorstep. Your eyes close and for a fleeting moment you understand the Universe in its simplest, most basic terms. Savor that moment, for your eyes open again and now you are drawn back to the reality – you are reading the introduction to a book on physical chemistry. If you are mildly perturbed at being returned to this apparently less appealing reality, you have just demonstrated a facility with a key and exquisitely valuable tool in the study of science, the *Gedanken experiment* (thought experiment). The use of thought trips will be of fundamental importance in the approach that this book takes toward understanding biophysical processes. That virtually any student has access to one of the most profound and sophisticated theoretical techniques available to a scientist is an important lesson to learn.

So here you are, just several pages into a textbook on biophysical chemistry and in clear possession of a sense that your imagination, rationally applied, is going to be a necessary tool for our studies. How can this be? Why not just write a text in which the facts about what is known are written down along with an honest appraisal of what has not been discovered yet (so that good fundable grants can be easily identified). In many cases this could be done to some reasonable degree of certainty, but how can you, the reader, be sure which of the facts you will study are (a) highly certain, (b) certain, or (c) just a little certain? Ultimately, all of the information is going to be relayed by a single source, so does that not imply a degree of confidence that you could apply to all the facts in the book. Are not facts facts after all? Is it not true that we know what we know, and the job of science is to simply extend the frontiers of our knowledge forward laying claim to the regions formerly unknown? Questions of this type are fundamental to the study of any scientific endeavor. Although it is unfortunate that the pop-culture treatment of questions about reality and certainty have to some degree reduced these questions to caricatures, they remain at the center of scientific inquiry about the world in which we live.

How do we know what we know about the organization of biological systems at the chemical level? The compelling pictures of macromolecules drawn in subnanometer resolution by a computer are in fact constructions deduced from patterns of scattered x-rays and have never actually been seen by the human eye or even any magnifying instrument that can form an image in the same fashion as the human visual system. How can we be so sure or even have any less doubt that one description is any better than any other? This is not a trivial point and in fact strikes to the heart of the study of knowing that obtained knowledge has any meaning in a real system or world. The study of knowing is called *epistemology* and is the field in which science and philosophy meet. The issues explored in epistemology are fundamental to an understanding of the method of science.

Derived from the Greek roots *episteme* (knowledge) and *logos* (theory), epistemology is essentially concerned with the theory of knowledge (i.e., what is the relationship between structure, origin, and criteria of knowledge). There are many important questions with epistemological roots of tangible and practical as well as intellectual interest to the scientist. For example, fundamental to human knowledge are issues of perception both in terms of sensory perception and misperception, the mode as well as choice of observables and the potential for perceptual illusion. A crucial issue is to define the relationship between the observer and the observed as well as the relationship between the knower (who may be other than the observer) and the object or system known. (The following example of Kepler is appropriate here, since Kepler modeled and proved his laws of planetary motion by using Tycho Brahe's superb data on the planetary positions. Brahe, although a good observer, had attempted to devise a set of celestial rules that depended on a lunar-geocentric alternative to the Ptolemaic and Copernican theories of the time. His formulation was non-sensical though his observations were accurate and without peer.) The types and kinds of knowledge as well as the degrees of certainty associated with each type of knowledge need exploration. The questions of what comprises truth, whether truth and understanding can be discovered, inferred or calculated, or if truth and understanding are different, are important modern questions of epistemology, and are argued among mathematicians and artificial intelligence, cybernetic, and intelligence-modeling workers. Even the nature, limits, and justification of inferences are important questions of epistemological nature.

2.6 The Beginnings of Modern Science– Kepler and Galileo

Johannes Kepler's approach to and formulation of the laws of planetary motion and Galileo Galilei's exploration of the laws of mechanics and motion mark not only the beginning of modern science but were instrumental in ending Aristotelian ways of knowing. Kepler's planetary laws are fundamentally important not only because of the result but for the shift he made in the premises of his arguments. In *Mysterium Cosmographicum*, Kepler argued that for an argument to be valid, it must be able to pass the test of observable experimentation. He wrote

> What we have so far said served merely to support our thesis by arguments of probability. Now we shall proceed to the astronomical determination of the orbits and geometrical considerations. If these do not confirm the thesis, then all our previous efforts shall have doubtless been in vain. (translation from Koestler, Arthur, *The Sleepwalkers* (New York: Macmillan, 1959, p. 255)

A practicing astrologer, Kepler was born in Germany in 1571. Ironically his interest in knowing the motion of the planets came from a desire for a more precise application of his magical beliefs in the influence of planets and stars on an individual human life. Since he believed in such cause-and-effect phenomena, his view of *causality* was radical for the time. Kepler proposed that the planets moved in their orbits because a force, "spreading in the same manner as light," came from the Sun and kept the planets in motion. Although Newton would show this concept (of anti-inertia) to be wrong, the idea *that things happen because of forces that are mechanical and can be measured* was groundbreaking. This view of causality implied that these mechanical forces could be observed, measured, and used to build a formal geometrical model that would be accurate, in terms of the forces (causes), in predicting the future (effects). It also implied that the application of equivalent forces on an equivalent system would yield equivalent results.

In a paradoxical way, Kepler was one of the pioneering biophysicists. He believed, without any significant evidence, that the mysterious forces of life could be influenced by the positions of the planets and the stars. As an astrologer he accepted that the forces acting between the celestial worlds and the living world of humans had a predictable pattern of correspondence. He believed that he understood the rules that governed the correspondence between human behavior and the positions of the planets. A knowledge of the mechanical rules of astrological forces was assumed. Thus, if he could know the actions (positions and movements) of the celestial bodies, he could apply his knowledge of the rules of interaction (the forces) and predict the effects on life events. By devising an accurate celestial physics he would be able to better understand biological processes. Today we would argue that his astrological rules are not well validated, and in fact we have replaced them with rules of chemistry and molecular cell biology. But the assumption that biological behavior can be understood via an understanding of the physical rules governing the Universe is the fundamental assumption of this book and modern biophysical chemistry.

When Kepler set out to explore the linkage between the physical nature of the Universe and biological systems, he was to attempt to build a formal model of the Universe that could represent the natural system (of planets and stars). What was different from the Aristotelian/Platonic and Ptolemaic tradition was that Kepler's formal model was validated not by what the mind thought should exist, but rather by empirical observation. Thus Kepler used the essential elements of modern scientific model building to develop his celestial mechanics:

(1) He studied a natural system by selecting a set of observables.
(2) The system is described by the specification of these observables and a characterization of the manner in which they are linked.
(3) Although theory may be applied to the problem, contact with the reality of the natural system is made wholly through the observables.
(4) A model can be constructed that formally relates the observables and their linkages such that a good formal model, under the proper circumstances, describes the original natural system to a prescribed degree of accuracy. The behavior of the model and the natural system is thus invariant with replacement of one for the other for a given proper subsystem.

We will explore more fully the nature of model building in Chapter 3. Even though Kepler did not apply his rules of building empirically validated models to his whole system (i.e., the astrologically based biophysical rules of interaction), his approach has been used and refined over the following centuries to replace these astrological rules. Because of his success in establishing a working, useful celestial mechanics, he set in motion the incredibly successful machinery of modern scientific investigation that ironically eventually invalidated his own set of beliefs with regard to the nature of life in our natural world. His failure to successfully advance the end result of a great astrology confirms his seminal contribution to the process of scientific discovery.

At the start of the twenty-first century, it is almost impossible for us to appreciate the icon-shattering nature of Kepler's treatment of astral motion. Kepler proposed and used observables to validate the idea that the path and motion of the planets was neither circular nor constant. The idea that the circle was perfect and that nature would naturally be dominated by a static perfect order was the idealizing belief of the Aristotelian mind that had dominated the intellectual perspectives for almost 2000 years. It is remarkable that Kepler was able to propose that the actual movement of the planets was elliptical and that their speed varied along these paths! It is inconceivable that his physics could have been convincing enough to be accepted if he had not used empirical observation to demonstrate the invariance of his formal model with the natural system. Not only did he establish the usefulness of model making as an effective methodology for discovering knowledge but he laid the groundwork for the dynamical modeling that has characterized modern scientific investigation.

While Kepler was the first biophysicist, Galileo was the first modern physicist. Born in Pisa, Italy in 1564, Galileo, like Kepler, developed and used the modern scientific method or progression of inquiry in his research into accelerated motion and dynamics. Galileo's major contributions were in mechanics and it was in these experiments that he made observations that were mapped to hypotheses expressed as mathematical models and then tested in carefully designed experiments. In his seminal work, *Discourses Concerning Two New Sciences*, he developed the field of mechanical dynamics starting with a definition of acceleration, making careful observations, and then reasoning from these experiences via the application of mathematical tools to arrive at important conclusions regarding motion and the strength of materials and structures. Galileo was the first thorough modern scientist practicing the progression of inquiry as evidenced by his use and emphasis on experimental models and experiment to test physical theory. He clearly recognized that experiment alone, though essential, did not constitute (modern) science since foundational ideas like acceleration transcended (formed the context or background) of laboratory experience. As a historical aside, Galileo is probably best known for his interest and views on astronomy. He gained the attention and displeasure of the inquisition though his firm and very public support of Copernican theory, especially after the appearance a supernova in 1604 which rocked the Aristotelian dogma of the immutable nature of the heavens. Kepler had little influence on Galileo (it was to be Newton who discovered the connections between planetary motion and the law of universal gravitation), but both of these early scientists can be credited with the discovery and application of the modern scientific method or progression of inquiry

2.7 Modern Biophysical Studies Still Follow the Paradigm of Kepler and Galileo

Within a context that will be a constant guide throughout this text, we now explore how the integration of the progression of inquiry into biophysical investigation can be summarized:

2.7.1 Describe the Phenomenon – What Is happening Here? What Are the Emergent Properties of the System?

The knowledge of a phenomenon depends greatly on the way in which it is observed. The choice of observables in the description of a system or in a process operating in a system is one of the most important steps in all science. Interestingly, we will learn that in classical mechanical treatments, the observables themselves are used to describe a system but in quantum mechanical treatments the description of the system depends on certain functions that *operate* on the observables. The use of operator functions to describe the linkages in a quantum mechanical treatment has important consequences and indicates that the observer is very strongly linked to the system under observation hence making independent or non-interactive observation difficult. Observations of systems and the development of methods to predict the behavior of the system under different conditions are important aspects of system science and are used extensively in thermodynamics. Thermodynamic treatments can be very useful when we are describing a system because they do not require a detailed knowledge of what is happening inside the system at all times. Thus certain tools let us use the very useful idea of a *black box*. A black box is a treatment of a system in which only the inputs and outputs are considered and these observables are linked phenomenologically. As a starting point, treating biological systems as black boxes is often a necessary first approximation or abstraction. Mathematical systems theory and thermodynamics are important physical tools at this stage. Studies of cybernetics, chaos, complexity and catastrophe theory, the multiple equilibria that describe ligand–receptor interactions, and the dependence of melting on cooperative interactions are all examples of biological application of these techniques. This is our starting point and we will take up the issue of the study of systems in Chapter 3.

2.7.2 Reduce the Phenomenon to a Systems Description: Identify the Components of a System – Who and What Is Involved? (What Are the Elements?)

Though we could conclude our study with a phenomenological analysis of a biological system, it is important and intellectually satisfying to have a more specific description of the components that make up a system. Many of the laboratory tools used to separate, concentrate, and characterize biomolecules are based on their physical properties such as size, shape, weight, and charge. The techniques sensitive to these properties are based to a great degree on mechanics, kinematics, and the transport phenomena of diffusion and charge movement. For the most part, these ideas are based on classical physics and include centrifugation and sedimentation, electrophoresis, chromatography, and the properties of viscous flow.

2.7.3 Analysis of Structure – What Does it Look Like? What Are the Relationships Between the Components? (What Are the Interaction Rules and What Is the Context of the System?)

In addition to identifying the components we also find it interesting to know how they are arranged and what their structure "looks" like. In biological systems, the description of the structure and properties of the chemical components alone is often not sufficient because these components are arranged into higher order structures such as membranes, organelles, and assemblies such as the electron transport chain. The ordering of these components into structures gives us a double benefit for having learned the physical principles outlined in the previous two sections. This is because the physical processes of transport, equilibrium, and systems analysis underlie the basis of cell biology and the physiology of the organism.

Being visual creatures, we tend to prefer to "see" the objects of our interest as we construct a picture of it in space (this includes linear, planar, three-dimensional, and multi-dimensional space). One of the most important techniques for visualizing structure is through the use of microscopy. Modern microscopy includes not only optical methods that use visible light to examine cells and tissues, but also adds methods that allow imaging of subcellular structures, molecules, and even atoms.

We are able to infer a great deal about the electronic and nuclear structure of molecules because of the interaction between electromagnetic radiation and matter. The theoretical explanation for these interactions, *quantum electrodynamics*, forms the basis of spectroscopy, which has allowed the chemical nature of biological systems to be explored in great detail. An understanding of basic quantum mechanics allows us to explore structure: electronic structure (through ultraviolet and visible spectroscopy); the structure that influences rotational and vibrational movements (through infrared, Raman, and microwave spectroscopy); structural influence on the magnetic spin properties of electrons and nuclei (through electron spin and nuclear magnetic spectroscopy); and the relationship between relativistic motion and structure (through Mössbauer techniques). Finally, because chemical structures can interact with electromagnetic radiation, twisting and scattering it, we gain structural knowledge from the techniques of Rayleigh scattering, polarimetry, circular dichroism, and x-ray crystallography.

We are able to use the physical models expressed in mathematical form along with the measurements of structure obtained from thermodynamics and spectroscopy to explore potential structures with the aid of a computer. A powerful relatively new tool available to the biological scientist is the ability to explore potential energy surfaces as biomolecules interact and find their preferred structure in an abstract state space (the space of possibilities). With the powerful visualization tools now available to most scientists, computational chemistry is a synthesis of art and science that has great theoretical and practical appeal.

2.7.4 Analysis of Dynamic Function – What Is the Mechanistic or Explanatory Cause of That?

Most of us are not satisfied to simply look at the system as a taxonomist might, pleased by a properly stuffed and static picture. In general we want to know how and why the system runs. In fact most of our modern interest in the structure of biological molecules and systems is the foreplay related to our passionate interest in function. Thus structure–function studies are the central goal of our investigations.

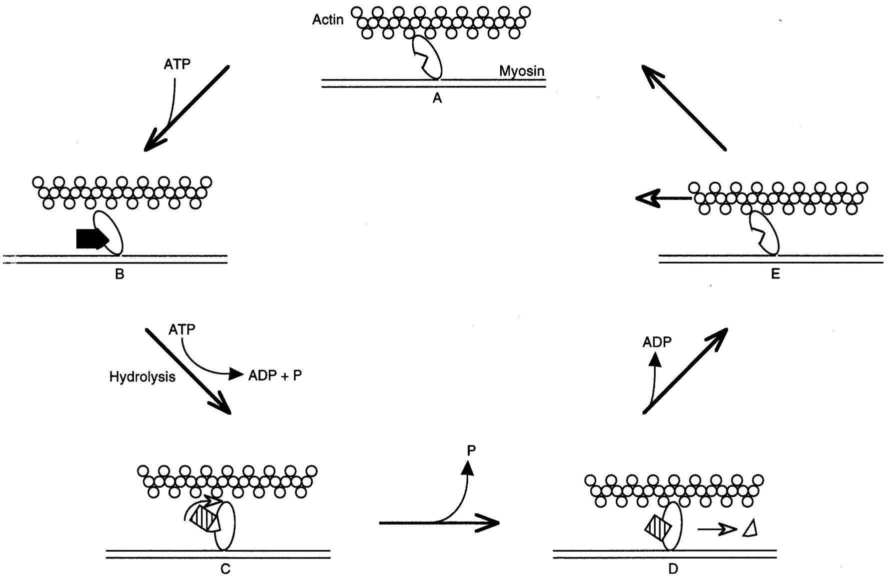

Fig. 2.1 Schematic of the molecular mechanical events in muscle contraction. As described in the text (**a**) the muscular elements are in the "rigor" state. (**b**) The non-bonding interactions between the myosin and actin are disrupted by the binding of ATP to the myosin. (**c**) With hydrolysis of the ATP, the myosin head straightens up. (**d**) When the inorganic phosphate is released, new interactions between the myosin and actin are generated. (**e**) The new intra-chain interactions induce the release of the ADP, which causes the myosin to return to its rigor conformation

The knowledge of how a system works at the molecular level, i.e., muscle contraction (Fig. 2.1), is satisfying because it connects the hidden clockwork to common observation. Mechanistically, a muscle fiber contracts because of the movement of the actin and myosin proteins with respect to one another. The shortening of the muscle follows activation by an electrical switching event, the depolarization of the neuromuscular junction. At the molecular level this shortening occurs as follows: At rest, a myosin molecule's "head" is bound tightly to the actin filament (the *rigor* configuration, from *rigor mortis* – the rigidity of death). The head is released from the actin filament when a molecule of ATP binds to a cleft in the head portion of the myosin thus inducing a conformational change in the myosin and weakening the rigor conformation. Hydrolysis of the bound ATP molecule into P_i and ADP is associated with a sudden straightening of the angle of the head thus causing the head to move nearly 5 nm down the actin fiber. There is a weak bonding interaction between the straight head and a new interaction site on the actin. This interaction causes another small conformational change which causes the P_i to be released from the head. The loss of the P_i releases a "power stroke" in which the myosin head moves back to the rigor angle releasing ADP because of the conformational change and thus pulling the actin fiber 5 nm into a new rigor conformation awaiting a new stroke cycle. Here form and function are elegantly interdigitated.

By exploring the details of molecular interactions, we now have an understanding of how the observables that we first discovered phenomenologically (muscles move) and characterized by a black box treatment with a state function (the force–length relationship of muscle contraction) occur. One of the important aspects of mechanistic studies is that they must give the same result as the black box treatment when adjusted for number, because the observables associated with the black box studies (usually thermodynamics) are generally more accurate. This is because there is a weaker coupling between observer and observed system and hence less opportunity for observer influence over the system (in Chapter 3 more will be said about this important subject).

We usually study systems mechanistically by observing how they change with a perturbation. Because systems at rest are in fact in dynamic equilibrium (this is a concept from statistical thermodynamics, i.e., a system is perturbed or moved away from equilibrium and then relaxes back toward the equilibrium state); the rate at which a system relaxes after being perturbed is the concern of kinetics. Methodologies that measure rates of chemical change provide a window into the response of a system to various perturbations. The molecular understanding of how quickly a system can move depends on a statistical thermodynamic formulation of how likely a perturbed or post-perturbed conformational state will be found. This is because the conformation of molecules and systems are *conservative systems*. Conservative systems are those in which the potential energy and hence the internal energy are related to the mechanical positions of the elements in the system. Since the direction a system moves after being perturbed depends on the energy flow and the energy flow depends on the potential energy gradients, form and function are tied tightly to one another. By studying kinetics we can examine structure from a different perspective and vice versa.

Finally, we can close the loop. Because we are interested in biological systems we are implicitly interested in how the system is integrated or controlled. What a system does and the rate at which it can do something is dependent on the energetics of its form and function. An active system is one that is perturbed away from its equilibrium state and hence its behavior depends on the potential energy surface near the equilibrium state or the next metastable state to which it will move. Controlling the potential energy surface is thus an obvious method of controlling the system. We can therefore speak to substantial quantitative terms about biological control systems if we understand the energetic interactions in a system that influence the potential energy or control surface. Since the cardinal interest of biophysical chemistry is to understand the energy relationships between the molecules and the systems in which they are found, it is obvious that biophysical chemistry is a natural language for understanding biological behavior and the systems that generate that behavior.

Further Reading

A variety of texts approach the interdisciplinary subject of molecular biophysics. Some are physical chemistry texts oriented to biological applications.

Cantor C.R. and Schimmel P.R. (1980) *Biophysical Chemistry, Parts I, II and III*. W.H. Freeman, New York.

Chang R. (2000) *Physical Chemistry for the Chemical and Biological Sciences*, 3rd edition. University Science Books, Sausalito, CA.

Chang R. (2005) *Physical Chemistry for the Biosciences.* University Science Books, Sausalito, CA.

Edsall J.T. and Wyman J. (1958) *Biophysical Chemistry*. Academic, New York.

Eisenberg D. and Crothers D. (1979) *Physical Chemistry with Applications to the Life Sciences.* Benjamin/Cummings, Menlo Park, CA.

Engel T., Drobny G., and Reid P. (2008) *Physical Chemistry for the Life Sciences*. Pearson-Prentice Hall, Upper Saddle River, NJ.

Tinocco I., Sauer K., Wang J.C., and Puglisi I. (2001) *Physical Chemistry (Principles and Applications in the Biological Sciences)*, 4th edition. Prentice-Hall, Englewood Cliffs, NJ.

There are an increasing number of new texts with a biophysics or physical biological approach. These are developing to support the increasing number of students with an interest in quantitative biology and bioengineering.

Beard D.A. and Qian H. (2008) *Chemical Biophysics: Quantitative Analysis of Cellular Systems*. Cambridge University Press, Cambridge.

Daune M. (1999) *Molecular Biophysics: Structures in Motion*. Oxford University Press, New York.

Jackson M.B. (2006) *Molecular and Cellular Biophysics.* Cambridge University Press, Cambridge.

Nelson P. (2008) *Biological Physics: Energy, Information, Life*. W.H. Freeman, New York.

Phillips R., Kondev J., Theriot J., and Orme N. (2008) *Physical Biology of the Cell.* Garland Science, New York.

Sneppen K. and Zocchi G. (2005) *Physics in Molecular Biology*. Cambridge University Press, Cambridge.

Waigh T.A. (2007) *Applied Biophysics: A Molecular Approach for Physical Scientists.* Wiley, Chichester.

The more traditional coverage of physical chemical principles can be found in the following texts. In general these texts are clear and lucid and are a useful place to start an exploration of topics outside the direct biological sphere. The newer texts have an ever increasing amount of biological material.

Alberty R.A., Silbey R.J., and Bawendi M.G. (2004) *Physical Chemistry* 4th edition. Wiley, New York.

Atkins P.W. (2006) *Physical Chemistry*, 8th edition. Oxford University Press, Oxford, New York.

Castellan G.W. (1983) *Physical Chemistry*, 3rd edition. Addison-Wesley, Reading, MA.

Moore W.J. (1978) *Physical Chemistry*, 4th edition. Prentice-Hall, Englewood Cliffs, NJ.

Philosophy and Epistemology

Feynman R.P., Leighton R.B., and Sands M. (1963) *Atoms in Motion, Lecture #1* **in** *The Feynman Lectures on Physics*, Volume 1. Addison-Wesley, Reading, MA. (In classic Feynman style he explains the approach to theory, experiment, observable and abstraction.)

Russell B. (1945) *A History of Western Philosophy*, Touchstone/Simon and Schuster, New York. (Fun to read and accessible discourse on philosophy for the non-professional philosopher. Bertrand Russell was a mathematician and his scientific tilt makes the scientist at ease with the subject.)

Muscular Contraction

Amos L.A. (1985) Structure of muscle filaments studied by electron microscopy. *Annu. Rev. Biophys. Biophys. Chem.*, **14**:291–313.
Pollard T.D., Doberstein S.K., and Zot H.G. (1991) Myosin-I, *Annu. Rev. Physiol.*, **53**:653–681.
Rayment I. et al. (1993) Three dimensional structure of myosin subfragment I: A molecular motor, *Science,* **261**:50–58.
Stossel T.P. (1994) The machinery of cell crawling, *Sci. Am.*, **271, 3**:54–63.

Problem Sets

1. A system can be described by listing the (1) overall or "emergent" properties, (2) elements that comprise it, (3) the way the elements are related to one another and to the background or context space, and (4) the characteristics of the contextual space. Write a systems description for several familiar scenarios: (a) a sports event or game, (b) a holiday dinner, and (c) a laboratory experiment.
2. Use a systems analysis to describe the system that Johannes Kepler studied.
3. For each model system developed in this book, make it a habit to write out the systems description whenever you encounter that model. This includes the kinetic theory of gases, thermodynamic systems, the Born model, the Debye–Hückel model, electric circuit models of electrochemical systems, etc.

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Bergethon, P.R.
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