Molecular Theory of the Living Cell

Sungchul Ji

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Concepts, Molecular Mechanisms,
and Biomedical Applications

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*To my wife, Jaehyun Lee,
without whose advice, love and encouragement,
this book could not have been born.*

Preface

There are three main objectives in writing this book – i) to summarize the key experimental observations on the living cell, ii) to develop a molecular theory of the living cell consisting of a set of concepts, molecular mechanisms, laws and principles, and iii) to apply the newly formulated theory of the living cell to solving concrete problems in biology and medicine, including the molecular mechanisms of force-generation in molecular motors (Chap. 8), morphogenesis (Chap. 15), the origin of life (Chap. 13), and evolution itself (Chap. 14).

The cell is arguably one of the most complex material systems in nature, in no small part because it is the building block of all living systems, including us. *We are cells, and cells are us*. To know how cells work, therefore, will contribute to understanding not only how our bodies work, which will advance medicine, but also how our mind works, which may help answer some of the age-old philosophical and religion-related questions from a new perspective. It is hoped that the molecular theory of the living cell presented in this book will contribute to the emergence of “the new science of human nature” that can lead “to a realistic, biologically informed humanism” (Pinker 2003). As a result of the research efforts of biologists around the world over the past several centuries, especially since the middle of the last century when the *DNA double helix* was discovered, we now have, as pointed out by de Duve (1991), a complete list of the components that constitute a living cell (e.g., see Table 17.2), and yet we still do not understand how even a single enzyme molecule works. There are tens of thousands of different kinds of enzymes in the human cell. We do not yet know how the cell expresses the right sets of genes at right times and right places for right durations in order to perform its functions under a given environmental condition.

Although many excellent books have been written on specialized aspects of the cell, such as the *Molecular Biology of the Cell* (Alberts et al. 2008), *Computational Cell Biology* (Fall et al. 2002), *Thermodynamics of the Machinery of Life* (Kurzynski 2006), and *Mechanics of the Cell* (Boal 2002), to cite just a few, there is a paucity of books that deal with the general principles, concepts, and molecular mechanisms

that apply to the living cell as a whole, with some exceptions such as Schrödinger's *What Is Life* written in the middle of the last century, Crick's *From Molecules to Men* (1966), Rizzotti's *Defining Life* (1996), and de Duve's *Blueprint of Life* (1991). The present book is probably the most recent addition to the list of the books on what may be called *theoretical cell biology* (in analogy to *theoretical physics*) that attempts to answer the same kind of questions raised by Schrödinger more than a half century ago (see Chaps. 16 and 21) and subsequently by many others.

During the course of writing the present book, I have often been reminded of a statement made by G. Simpson (1964) to the effect that physicists study principles that apply to all phenomena; biologists study phenomena to which all principles apply. For convenience, we may refer to this statement as the *Simpson thesis*. More recently, I came across another truism which may be referred to as the *de Duve thesis*: The problems of life are so fundamental, fascinating and complex that they attract the interest of all and can be encompassed by none (de Duve 1991, Preface).

True to the *Simpson thesis*, the present work deals with unusually wide-ranging topics, from inorganic electron transfer reactions (Sect. 2.2), single-molecule enzymology (Sect. 11.3), gene expression (Sect. 12.9), morphogenesis (Chap. 15), category theory (Chap. 21), the origin of life (Chap. 13), biological evolution itself (Chap. 14), personalized medicine (Chap. 18), to drug discovery (Chap. 19). True to the *de Duve thesis*, the readers will find numerous gaps in both the kinds of topics discussed (e.g., photosynthesis and immunology) and the factual details presented in some of the topics covered, reflecting the limitations of my personal background (as a physical-organic chemist-turned-theoretical-cell-biologist) in experimental cell biology and mathematical and computational skills.

Two revolutionary experimental techniques appeared more or less simultaneously and independently in the last decade of the twentieth century – the *DNA microarrays* (Sect. 12.1) (Watson and Akil 1999) and the *single-molecule manipulation and monitoring techniques* (Sect. 11.3) (Ishii and Yanagida 2000, 2007, van Oijen and Loparo 2010). With the former, cell biologists can measure tens of thousands of mRNA levels in cells simultaneously, unlike in the past when only a few or at most dozens of them could be studied at the same time. The DNA microarray technique has opened the window into a whole new world of complex molecular *interactions* underlying the phenomenon of life at the cellular level (see *interactomes*, Sect. 9.3), the investigation of which promises to contribute to deepening our understanding of the phenomenon of life as well as the phenomenon of mind on the most basic level (Pattee 1982, Thompson 2009).

In contrast to the DNA microarray technique which provides a global view of cell metabolism, the single-molecule measuring techniques (Ishii and Yanagida 2000, 2007, van Oijen and Loparo 2010) make it possible to probe cell metabolism at the level of single enzyme or DNA molecules. The single-molecule mechanical measurements are truly amazing, since, for the first time in the history of science, it is now possible to observe and measure in real time how a single molecule of *myosin*, for example, moves along an actin filament utilizing the free energy supplied by the hydrolysis of a single molecule of ATP (see Panel D in Fig. 11.33).

The theoretical investigations into the molecular mechanisms of *oxidative phosphorylation in mitochondria* that I began in 1970 as a postdoctoral fellow under David E. Green (1910–1983) at the Institute for Enzyme Research, University of Wisconsin, Madison, had led me to formulate the concept of the *conformon* in 1972–1985 (see Chap. 8) and the *Principle of Slow and Fast Processes* (also known as the *generalized Franck-Condon principle*) in 1974 (Sect. 2.2.3) and construct what appears to be the first *theoretical model* of the living cell called the *Bhopalator* in 1985 (Sect. 10.1). These theoretical models and related theoretical ideas and principles are summarized in this book, and an attempt has been made to apply them to analyze some of the rapidly expanding experimental data generated by the two revolutionary techniques mentioned above. In addition, these theoretical results have been utilized to formulate possible solutions to many of the basic problems facing the contemporary molecular, cell, and evolutionary biology.

When I formulated the concept of the *conformon* in 1972 (see Chap. 8) in collaboration with D. E. Green, I did not realize that I would be spending a good part of the next four decades of my life doing theoretical research on this concept and related physical, chemical, and philosophical principles, including the *generalized Franck-Condon principle* (GFCP), or the *Principle of Slow and Fast Processes* (PSFP) (Sect. 2.2). If *conformons* do indeed exist in biopolymers as appears likely on the basis of the currently available experimental data and theoretical considerations (see Chap. 8 and Sect. 11.4), the following generalizations may hold true:

1. The cell is an organized system of *molecular machines*, namely, biopolymers (DNA, RNA, proteins) that carry out microscopic work processes including enzymic catalysis, active transport, molecular motor movement, gene expression, DNA repair, and self-replication.
2. Conformons are packets of mechanical energy stored in sequence-specific sites within biopolymers derived from *chemical reactions based on generalized Franck-Condon mechanisms* (Sect. 8.4).
3. Therefore, the living cell is a supramolecular machine driven by chemical reactions mediated by conformons.

These statements can be schematically represented as follows:

The most recent and most direct experimental verification to date of the conformon concept was reported by Uchihashi et al. (2011, Junge and Müller 2011; see Sect. 7.1.5) who, using the high-speed atomic force microscopy, succeeded in visualizing the propagation of the conformational waves (or *conformons*) of the β subunits of the isolated F_1 ATPase stator ring. It now appears that the conformon concept has been verified more than four decades after it was proposed by Green and Ji (1972a,b, Ji 1974, 1991, 2000; Chap. 8 in this book).

In (Ji 1991), conformons were postulated to mediate what I elected to call *the cell force*. The cell force was invoked to account for the *functional stability* of the living cell in analogy to the strong force which was invoked by physicists to account

for the *structural stability* of the atomic nuclei (Han 1999; Huang 2007). One of the most significant findings resulting from writing this book, I believe, has been the recognition that the whole-cell RNA metabolic data measured with microarrays may provide the first experimental evidence for the cell force. This is discussed in Chaps. 12 and 13.

My desire to test the validity of Scheme (0–1) as objectively and as rigorously as possible has led me to explore a wide range of disciplines during the past four decades, including not only biology, physics, chemistry, engineering, and computer science but also mathematics, linguistics, semiotics, and philosophy. The numerous principles, laws, and concepts that I have found necessary to account for the phenomenon of life on the molecular and cellular levels have been collected and explained in Part I of this book. Part II applies these principles, laws, and concepts to formulate a comprehensive *molecular theory of life* which I have at various times referred to as *biognergetics* (Ji 1985), *biocybernetics* (Ji 1991), *microsemiotics* (Ji 2002a), *molecular information theory* (Ji 2004a), and *renormalizable network theory of life* (Sect. 2.4), depending on the points of emphasis or prescinding (to use a Peircean idiom (Sect. 6.2.12)). The molecular theory of life developed in Part II is then utilized in Part III to formulate possible solutions to some of the basic problems facing the contemporary molecular and cell biology, including the definitions of the gene and life, mechanisms of molecular machines, morphogenesis and evolution, and the problems of interpreting DNA microarray data (Ji et al. 2009a) and the single-molecule enzymological data of Lu, Xun, and Xie (1998); Xie and Lu (1999); and Ishijima et al. (1998). Possible applications of the molecular theory of the living cell developed in this book to drug discovery research and personalized medicine are also included in Chaps. 18 and 19.

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After obtaining a Ph.D. degree in physical organic chemistry from the State University of New York at Albany in 1970 and having taught chemistry at the Mankato State College for the previous 2 years while writing my thesis, I embarked on an unusually long postdoctoral journey, from 1970 to 1982, doing research successively in theoretical bioenergetics and mitochondriology (Enzyme Institute, University of Wisconsin, Madison), experimental biophysics (Johnson Research Foundation, University of Pennsylvania School of Medicine, Philadelphia), micro-circulation physiology and tissue photometry (Max Planck Institute of Systems Physiology, Dortmund, West Germany), and organ and biochemical toxicology (Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill). I want to thank David E. Green, Britton Chance, Manfred Kessler, and Ronald Thurman for their professional guidance and support for my research during these years.

Since coming to Rutgers in 1982, my research efforts have benefited from the light teaching and administrative duties placed on me and from the free and friendly scholarly atmosphere of the Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy (EMSP), fostered under the leadership of Deans John L. Colazzi and Christopher Molloy and Chairs Robert Snyder and Debra Laskin. My research in experimental and theoretical toxicology and cell biology was also aided, directly or indirectly, by many of my colleagues at EMSP, including Fredrick Kauffman, Kenneth Reuhl, Mike Iba, and Andrew Gow, and by the many bright

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