Preface

About 80 years ago, one of the pioneers of quantum mechanics, Schrödinger, published the seminal work *What Is Life?*, in which he predicted the properties of DNA as an information-carrying molecule and discussed the importance of nonequilibrium. This work was an attempt by a physicist to uncover the universal properties of life and played a significant role in the rise of molecular biology. With its advance, the properties of individual molecules within living organisms are revealed. However, the mere presence of specific molecules, such as nucleic acids or proteins, does not mean that something is alive. We need to understand how a collective of molecules creates a dynamic living state.

Let us rephrase the question *What is life?* to *Can we reveal the universal properties of a macroscopic life system of such a collective of molecules and formulate a systematic theory for it?*. Although this may still seem a difficult question to answer, mankind once succeeded in developing a macroscopic phenomenology for a system of collective of molecules, *thermodynamics*, by restricting our concern to stable equilibrium states. Now, instead of thermal equilibrium, let us focus on a robust living state. Can we extract universal properties from it, discover general laws in it, and formulate a macroscopic theory for it? This is the question addressed in this volume.

Living organisms generally form a hierarchy: Molecules assemble to form cells, cells assemble to form individual organisms, and individuals assemble to form an ecosystem. In this book, instead of examining each molecule or cell individually, we will consider the fundamental properties of reproduction, heredity, adaptation, memory, development, and evolution by emphasizing the principle of consistency across hierarchical levels, such as the collective of molecules versus a cell. First, we will reveal the nature of the nonequilibrium state that sustains living organisms and search for the laws that govern cell growth. Next, we will investigate how the seemingly contradictory properties of plasticity (the ability to change in response to environmental changes) and robustness (the ability to maintain internal stability)

are compatible in a living system. We will explore adaptation, memory, and evolution by considering the consistency between phenomena occurring on different time scales. We will also uncover general principles of multicellular organisms, where interacting cells differentiate into different types to form a stable tissue or organism. Finally, by linking plasticity to fluctuations, we will unveil the direction and constraints in the evolution of a biological state (phenotype) that cannot be explained by random genetic mutation and selection alone.

Of course, the goal of this book – to understand the universal properties of life, comparable to thermodynamics, or to create a filed of "universal biology" – cannot be achieved overnight. Here I have used the term "universal biology," which may be unfamiliar to most readers. As far as I know, this field was first proposed in the science fiction novel *Who Will Inherit the Earth?* by Sakyo Komatsu. In this novel, universal biology is defined as a field that seeks to understand the universal properties of life, not only restricted to those that have evolved on Earth but also including those in the universe or in synthetic protocell systems as we are exploring today. In this novel, published in 1968, researchers in the twenty-first century explore the universal principles of possible patterns of life. How close have we come to this novel of half a century ago? This book may also be a report to the late Sakyo Komatsu.

Life is a unique state characterized by *having a variety of components, maintaining its state, and having the ability to reproduce*. Can we discover a state equation that represents this universal class? Can we uncover the principles of reproduction, adaptation (the compatibility of plasticity and robustness), memory (the creation of inherent time and history), differentiation (the tendency to diversify into different types, whether in cells or species), and evolution (the feasibility and constraints of phenotypic change)? I hope this book will serve as a first step in considering these questions.

In 2003, I published *What Is Life?* in Japanese, the English version of which was published in 2006. The Japanese version has sold over 10,000 copies. Encouraged by this support and motivated by the progress in the field over the past 20 years, I have written this volume. In this volume, readers will find that the names of genes or molecules are rarely mentioned. Although I discuss biological experiments, the focus is not on the molecular details but rather on how we can extract the universal properties of living systems from the experimental results. The theoretical discussions are based on mathematics and physics together, with the results of computer simulations. However, the focus is not on equations or specific models – one can skip them – but on exploration of the logic how a robust living state emerges in dynamic systems with a large number of components.

Chapters 1 and 2 provide an overview of the goals and methods of universal biology. I present five methodologies, emphasizing the interplay between

microscopic entities (e.g., molecules) and robust macroscopic states (e.g., cellular states): (i) phenomenological theory for a robust macroscopic state (cells, organisms), (ii) exploration of universal statistical laws at the microscopic level (e.g., molecules for a cell, cells for an organism), (iii) extraction of characteristic properties as a result of consistency between the macroscopic states and constituent microscopic units that exist at different spatiotemporal scales, (iv) experimental approaches that pay attention to such macro–micro relationships, and (v) consequence of violation of macro–micro consistency leading to aberrant biological states. Following this general framework, the book explores topics such as cell reproduction and the origin of life (Chapter 3), the adaptation process of organisms balancing plastic change and internal robustness (Chapters 4 and 5), kinetic memory (Chapter 6), cell differentiation and development (Chapter 7), the relationship between fluctuations and evolution (Chapter 8), and the constraints and directionality in the evolution of biological state (phenotype) (Chapter 9). Chapter 10 discusses ongoing or future studies, including the origins of life, endosymbiosis and multicellular organisms, the resilience of ecosystems, possible correlations between developmental and evolutionary processes, and the dynamic memory and learning of the brain, all from the perspective of consistency across hierarchical levels. The chapter concludes with a discussion of the mathematical framework needed to address the issues presented in this book.

I have designed this volume so that, after reading Chapters 1 and 2, you can move on to any of Chapters 3 through 9, depending on your interests (though it is ideal to read Chapters 4 and 5 together, and the same for Chapters 8 and 9). Of course, reading the entire volume in that order is recommended. If parts of Chapters 1 and 2 seem too abstract or difficult, feel free to skip them for now and return to them after reading the later chapters.

While a full understanding of the research presented in this volume may require some knowledge of analysis in dynamical systems theory with mathematical equations, one does not necessarily need to follow the equations to grasp the essence. However, since some readers (especially those with a background in physics) may find the equations helpful, I have included them in some sections. But again, you can skip them and still understand the essence. I hope you can appreciate the book according to your own interests and background.

This book could not have been completed without the help of many people. First, I would like to express my deep gratitude to the Japanese people who have continuously supported the present research through research grants and support from the Center for Complex Systems Biology and the Universal Biology Institute at the University of Tokyo (2017–). The support from Novo Nordisk Foundation and Niles Bohr Institute from 2022 is also very much appreciated.

I am also deeply grateful to Professors Yuzuru Fushimi, Toshio Yanagida, and Akiyoshi Wada, and to the late Professor Fumio Osawa for their continuous encouragement. This book is the result of numerous collaborative research projects with many colleagues and students, including Tetsuhiro Hatakeyama, Yuichi Wakamoto, Saburo Tsuru, Masayo Inoue, Yusuke Himeoka, Nobuto Takeuchi, Atushi Kamimura, Yuuki Matsushita, Takahiro Kohsokabe, Tomoki Kurikawa, Jumpei Yamagishi and Riz Noronha. Special thanks are due to Professor Chikara Furusawa, who could almost be considered a coauthor, for the close, stimulating, and collaborative research over 25 years. Although I cannot mention everyone by name, I would also like to thank all the other collaborators and members of my research laboratory for their invaluable help. I am deeply grateful to all of them.

Most of this book is based on lectures and seminars on Universal Biology that I have given to date. Along with the establishment of the Universal Biology Institute at the University of Tokyo, I started a course on Universal Biology at the Graduate School and have been giving this course for eight years to students in physics, biology, bioinformatics, and so on, while giving some lectures at the Graduate School of Frontier Biosciences at Osaka University, Hokkaido University, Kyoto University, and Ochanomizu University, as well as seminars for high school students and public lectures. In addition, I have presented the contents of the preset volume in a two-week lecture course at the International Center for Theoretical Physics in Trieste, as well as at schools or conferences in Italy, Denmark, Germany, France, Spain, Ireland, Armenia, Argentina, the United States, India, China, and so forth. The stimulating feedback I received from students and participants was a tremendous help in completing this book.

Some parts of this book were developed during my visits to various institutions. I am particularly grateful for the hospitality of the Institute for Advanced Study in Princeton. Of course, the continued support and stimulating discussions with members of Universal Biology Institute at the University of Tokyo and the Biocomplexity Group at the Niels Bohr Institute have been of great help in completing this book, and I am truly grateful to all involved.

Most of the present volume is based on my book *Universal Biology* (Fuhen seibutsugaku in Japanese). I am grateful to the University of Tokyo Press for the kind permission. For the cover of this book, I chose to use "Bird and Animal Screens" by Ito Jakuchu 1716–1800. I am grateful to Shizuoka-prefectural museum for allowing the use of the picture. The picture vividly represents dynamics and diversity of life with interaction among species. Universal biology seeks to uncover the universal laws and properties that apply for diverse life. With the picture, I hope one can sense the stirring of the new field we are developing in the volume.