Preface

The completion of human genome sequencing was an epoch-making event in reductionism biosciences, liberating a vast amount of experimental data and allowing us to relate specific parts of it to genes. The challenge for the biosciences in the twenty-first century is to integrate this information into a better understanding of biology, physiology, and human pathology. The integration is moving the world toward a new generation of bioscience and bioengineering, where biological, physiological, and pathological information from humans and other living animals can be quantitatively described *in silico* across multiple scales of time and size and through diverse hierarchies of organization - from molecules to cells and organs, to individuals. The physiome and systems biology represent such emerging biosciences. Such new trends in biosciences share a common direction, namely, an "integrative" approach that allows us to understand mechanisms underlying biological and physiological functions that emerge through the dynamics of each element and large aggregations of those elements.

The title of this textbook, *Harnessing Biological Complexity,* comes from the fact that we have a huge number of biological elements at hand - molecules, cells, and organs - and we are aware that each of them behaves in a more-than-simple way owing to its complex structure and the nonlinear dynamics governing its behavior. Moreover, an aggregation of specific elements behaves as a system. Thus, we are required to "harness" that complexity in terms of both the huge number of elements and their dynamics so that we can achieve an understanding of the mechanisms responsible for biological and physiological functions. Toward this end, integrative biosciences and bioengineering in their early stages aim at establishing frameworks and information infrastructures for describing biological structures and physiological functions on multiple scales of time and space. Next comes databasing and sharing, because it is not realistic to expect that a single research lab can find comprehensive answers to all the important questions. International communities such as those for systems biology markup language (SBML), CellML, JSim, Virtual Physiological Human (VPH), and the Neuroinformatics platforms of the International Neuroinformatics Coordinating Facility (INCF) have made pioneering efforts to establish those frameworks. In this textbook, we will use such a public platform, found at www.physiome.jp, which is being developed in communication with these other efforts mentioned above. The platform is capable of representing the hierarchical,

modular, and morphological structure of physiological entities and functional operations (influence) of one element on other elements. The platform provides a software program called *insilico*IDE (ISIDE) which can take on the roles of a model composer, a model browser, and a model simulator for models written in an XML format such as *insilico*ML (ISML) which is used in physiome.jp, SBML, and CellML. The platform has also a set of databases, *insilico*DB (ISDB), including ISML-ModelDB, MorphologyDB, and Time-seriesDB. The platform can thus enhance the stream of model sharing and increase the diversity of building blocks useful for integration.

Because biological and physiological functions are realized dynamically over time, it is inevitable that we have to describe any one of them using mathematical equations if we are to understand them quantitatively. We perform mathematical modeling and computer simulations of a model for the function that is under consideration. Hence, this textbook is written as a brief introduction to computational biology and physiology. Chapter 2 is on modeling at the cellular level, where we consider several examples from electrophysiology. In Chap. 3, we deal with cellular networks as models of tissues and organs. In both those chapters, we guide the reader to grasp the physical and mathematical background of each of the models provided and then to perform computer simulations on the models, to provide a deeper understanding of what is involved. The use of advanced physics and mathematics is limited so that the textbook will be accessible to biologists and physiologists; illustrative details are provided when necessary. Nevertheless, it will be helpful for the reader to have at least a basic knowledge of physics and mathematics as taught at the first-year level of college. Simulations in the examples can be performed easily because ISML files defining most of the models used in this textbook can be downloaded from ModelDB at www.physiome.jp. Once *insilico*IDE has been downloaded, the reader can just open a model file to simulate the dynamics of the model. The reader can then alter parameter values and equations and construct her or his own models to examine how they behave. The reader can also learn to use the platform, including *insilico*IDE, in Chaps. 4 and 5, where there are more examples. After becoming familiar with the use of the platform, the reader can try to construct a large-scale model for research purposes by combining the existing models in the model databases at ModelDB of physiome.jp, the model repository of CellML, and BioModels of SBML. In this way, new models can be created on *insilico*IDE, and both existing and new models can be combined, meaning that we are going to achieve a systematic way for harnessing biological complexity.

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