Chapter 1

Looking for a Mathematical Theory of Biological Systems

1.1 Introduction

This monograph tackles the ambitious aim of developing a mathematical theory of biological systems focused on ageing, degeneration, and repair of biological tissues under individual self-repair actions that may also involve advantage of medical actions and therapies. More precisely, this chapter provides a brief description of the aims, contents and organization of the monograph, organized as Lectures Notes. Specifically, it introduces the concept of mathematical theory of complex biological systems and describes the sequential steps to pursue the aforesaid objective. Of course, the authors do not naively claim that such objective is effectively achieved. Simply some perspective ideas, and some preliminary steps, are brought to the attention of applied mathematicians.

As is known, mathematical models attempt to describe, by means of equations, the dynamics in time and space of real systems that, in the case under consideration, belong to living matter. All mathematical models need to identify the parameters that appear in the equations. Once this assessment has been properly performed, the model can be used to provide an approximate description of a physical reality. In some special cases, the model can even depict emerging behaviors that are only partially shown by empirical data. Finally, it contributes to the refinement of experiments.

The modeling of biological systems needs to tackle the additional difficulty generated by the particular features of living matter. Among the various issues that will be critically analyzed in the next chapter, the lack of invariance principles that are typical of the inert matter systems. A critical analysis of this topic has been developed in the papers [Herrero (2007)], [May (2004)], and [Reed (2004)], see also [Hastings and Palmer (2003); Hastings *et al.* (2005)].

The paper by Hartwell *et al.* [Hartwell *et al.* (1999)] proposes a deep insight into the above issues and searches for a constructive interplay between the naive enthusiastic attitude of some applied mathematicians and the unreasonable scepticism of others. The main conceptual idea is that invariance principles are modified by the ability of living systems to express specific strategies that depend on survival purposes and adaptation to environmental conditions. Therefore, living systems have the ability to extract energy for their own well-being. Moreover, their adaptation ability generates mutations which occur at the molecular scale of genes and induce phenotype mutations. This evolution may even be very rapid in some specific pathologies.

It is worth stressing that the conclusive phrases of [Hartwell *et al.* (1999)] would seem to encourage a constructive interaction between biological and mathematical sciences. This concept is also related to the expectation of the scientific community which in this century, has been looking for a mathematical formalization of phenomena in life sciences that will be analogous to the mathematical formalization that characterized the progress of science over the last two centuries essentially devoted to the interaction between mathematical and physical sciences.

The above reasonings have motivated the contents of this monograph, whose main objective is to develop a mathematical theory of complex biological systems focusing on some specific systems, such as wound healing and repair, as well as some aspects of cancer phenomena. The concept of the mathematical theory is given in the next section. However, it is worth stating that we do not claim that this ambitious aim has been fully achieved; on the other hand, we hope that some preliminary results have been obtained and that this monograph offers guidelines for future developments.

1.2 On the Concept of Mathematical Theory

Let us first focus on the concept of the ***mathematical theory of biological systems***, which should be clearly distinguished from that of ***mathematical model***, whose derivation is based on conservation or equilibrium equations. Generally, these relations correspond to causality principles, closed by ***phenomenological models*** that describe the behavior of the matter. Mathematical models can be derived at any of the observation and representation scales that are typical of biological systems, namely molecular, cellular, and tissue scale.

Although tissues correspond to the largest macroscopic scale, the concept of ***network*** should be added as it technically refers to organs, where tissues are organized into complex systems that develop high-level specific functions that are connected through networks. The dynamics and the interplay among these networks is ruled at the lower cellular and molecular scales.

A mathematical theory should obtain the aforementioned material behaviors through a robust theory, delivered by biological sciences, that is suitable to transfer the information delivered at the molecular scale to the cellular scale. The mechanics of tissues is determined by the dynamics of cells, which are generated by the molecular dynamics. These concepts are reported in [Bellomo and Delitala (2008)] that focused on cancer phenomena, but they can easily be extended to a large variety of biological systems.

From the above reasoning, it is plain that the theory should specifically capture the multiscale aspects of all biological phenomena and select the correct mathematical framework to deal with the modeling at each scale. Subsequently, methods to link models at each scale have to be developed, for instance that of cells with those at the corresponding lower (genes) and higher (tissue) scales.

Considering that the existing mathematical methods have not yet been able to identify a uniquely defined approach, it is worth trying to understand why scientists are still far from developing a biological mathematical theory analogous to those of mathematical physics that have been developed over the last century. These concepts are specifically focused on the degeneration and repair of biological tissues, and, when appropriate, they are related to ageing phenomena.

1.3 Plan of the Monograph

After the previous preliminary introduction, the contents of this monograph, which is organized into nine more chapters, can be given.

- Chapter 2 deals with the analysis of the complexity characteristics of biological systems viewed as living systems. A reduction in complexity requires, as we shall see later, on the decomposition of the overall system into functional subsystems as the first step towards the development of the approach of systems biology. Subsequently, the approach derives evolution equations for each subsystem and the links among them to model the evolution of the overall system.

The other eight chapters are subdivided into three parts.

Part I is devoted to a phenomenological description of the class of biological systems under consideration in view of the mathematical approach proposed in the second and third parts of the monograph. A general strategy is identified, which is based on the concept that new mathematical tools should be developed to constrain the complexity features of living matter in equations, to the greatest possible extent.

- Chapter 3 presents a phenomenological description of the immune system, which plays an important role in the biological processes treated in the monograph (and, of course, in many other, if not all, processes). Specifically, this chapter is necessary for a deeper understanding of the subsequent one, which is devoted to the specific biological phenomena under consideration. The description is also inspired by the functional decomposition introduced in Chapter 2. Therefore, the components of the system are identified properly and analyzed focusing on the biological functions they express. The contents first introduce the role of bacteria and viruses, subsequently identify the main components of the immune systems, and finally analyze the respond of the immune, namely adaptive and acquired immunity. The presentation does not claim to be exhaustive. It simply aims at offering to applied mathematicians an overall presentation containing a reduced amount of information, which appears necessary to develop the modeling approach.

- Chapter 4 provides a phenomenological analysis of the wound healing process, in view of the development of the mathematical approach which needs a detailed focusing on well defined biological phenomena, so that it can be described by mathematical equations. The applications treated in Part III specifically refer to this chapter.

- Chapter 5 analyzes the different levels of organization related to the observation and representation scales from genes and mutations to wound healing, organ repair, and fibrosis diseases induced by cell mutations. The various concepts of the immune system introduced in Chapter 3 are here used for the aforementioned phenomenological description. This chapter also defines the general strategy that will be followed to pursue the objective of deriving a mathematical theory according to the approach of systems biology.

Part II provides a survey of the mathematical tools that will be used for the modeling applications. The contents takes advantage of the system biology approach and of the modeling strategy elaborated in Part I. The presentation focus on a revisiting and some developments of the existing literature in the field addressed to the specific aims of these Lectures Notes and to the applications that have been selected in Part III as case studies.

- Chapter 6 presents the derivation of the mathematical structures of the kinetic theory for active particles, known as the KTAP theory (for short), which is suitable to describe the dynamics of large systems of interacting living entities [Bellomo, Bianca, and Delitala (2009)]. This chapter also shows how the mathematical structures can be used towards the modeling at low scales, namely genes and cells which are regarded as independent systems. An introduction is above proposed from the applied mathematicians viewpoint, concerning the interpretation of the complex dynamics of immune competition. The analysis is developed at the cellular scale.

- Chapter 7 deals, at a methodological level, with the crucial problem of linking the dynamics from the small to the large scales, namely from genes to cells and from cells to tissues. Preliminarily, some phenomenological models of tissues are briefly reviewed to offer a panorama of the phenomenological models that will be compared with those derived from the underlying description at the cellular level. Subsequently, the mathematical asymptotic methods to derive macroscopic equations from the underlying equations at the microscopic scale, are presented. The method still needs some further developments of the tools presented in Chapter 6. The contents of this chapter complete the presentation of the mathematical tools and structures that can act as a general paradigm to derive specific models, and ultimately a biological mathematical theory.

Part III selects and develops some specific applications chosen according to the authors' bias. Moreover, it critically analyzes the central problem of deriving a mathematical theory of biological systems. Specifically, the strategy proposed in Part I is used to refer to the results obtained with the mathematical approach so that a variety of open problems are identified and brought to the attention of the reader.

- Chapter 8 deals with the application of the above mentioned approach to the analysis and the modeling of a specific biological phenomenon, namely the formation of a keloid triggered by viruses and the genetic susceptibility of a patient. The role of the immune system is also considered in this chapter, which also analyzes the possibility of the further degeneration of tissues related to inflammation followed by mutations that result in the onset of malignant phenomena.

- Chapter 9 shows how the methods mentioned in Chapter 7 can be developed properly and applied to derive models at the macroscopic scale, focusing on chemotaxis. This approach is an alternative to the classical continuum mechanics methods based on conservation equations closed by models of the material behavior of biological tissues. The application focuses on the derivation of chemotaxis models that play an important role in the wound healing processes.

- Chapter 10 proposes a critical analysis of the overall contents of the monograph. The various issues, developed in the preceding chapters, are viewed from a biological mathematical theory point of view, which is the main objective of this monograph. The critical analysis points out the conceptual difficulties which needs to be overcome towards the afore-said challenging research program.

The appendix offers some additional tools pertaining to the kinetic theory for active particles that are not specifically used in this monograph but which could be useful for further developments and applications. Several biological terms that should make applied mathematicians more acquainted with some topics of biological sciences are presented in a glossary. The glossary is not limited to the terms used in the monograph. Various terms has been added to improve the overall knowledge of the reader.

It is worth mentioning that the conceptual difficulty of the topics under consideration have motivated the design of new mathematical tools such as new concepts of system biology and further developments of the KTAP theory. The aim is twofold: to provide a new conceptual background and research perspectives for applied mathematicians involved in the challenging research field of mathematics for living systems, and to offer Lecture Notes for advanced courses in mathematical biology.