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*Editorial*

# Interplay and multiscale modeling of complex biological systems

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**Abstract:** Recently the understanding of complex biological systems has been increased considering the important interplay among different scholars coming from different applied sciences such as mathematics, physics and information sciences. As known, the modeling of a complex system requires the analysis of the different interactions occurring among the different components of the system. Moreover, the analysis of a complex system can be performed at different scales; usually the microscopic, the mesoscopic and the macroscopic scales are the most representation scales. However, a multiscale approach is required. A unified approach that takes into account the different phenomena occurring at each observation scale is the desire of this century. This editorial article deals with the topic of this special issue, which is devoted to the new developments in the multiscale modeling of complex biological systems with special attention to the interplay between different scholars.

## Preface

In the last two decades, the research activity in biology has shown the important interplay between different scientists in order to gain information in the modeling and analysis of complex phenomena occurring in the real world. In particular, complex biological systems have gained much attention and the interplay among mathematicians, physicists and information science scholars on the one hand and biologists, immunologists, physicians on the other hand have increased. Moreover, the different

international calls for interdisciplinary projects have extensively allowed the interactions and the collaborations among the different scholars coming from the different sciences and the different countries. Consequently, new hybrid research domains and scholars have raised and the management of complexity has been more easily pursued and achieved.

The complex emerging behaviours in biological systems are the consequence of nonlinear interactions among a large number of elements composing the biological system [1,2]. A biological system is usually composed by molecules, cells, and tissues (see the books [3]) whose global interaction is not the linear sum of each interaction. The analysis of complex biological systems thus requires a particular attention and is usually performed in three steps: A theoretical analysis (or phenomenological analysis), a computational analysis (or modeling analysis) and a numerical or experimental analysis (or validation analysis). This approach is nowadays well-developed and the main contributions in the pertinent literature refer, among others, to the tumor growth and immune system competition [4], soft tissues growth [5], fibroproliferative disorders [6], genoma analysis [7]. In particular many of the above mentioned applications have been obtained as result of the collaboration of mathematicians and physicists with scholars coming from the biological and medical sciences. The outcome of these interplays has been the birth of new hybrid research fields, among others, biomathematics, bioinformatics, biomechanics, and biophysics.

**Biomathematics.** This research domain is mainly the result of the interplay between biologists and mathematicians. Specifically, the biological system under consideration is modeled by employing a system of mathematical equations, usually differential equations (ordinary or partial differentential equations) and/or algebraic equations. In this context the system of mathematical equations is called 'a model' and the solution describes the time and space evolution of a quantity related to the system [8]. Accordingly assumptions and parameters are defined and the evolution of the system is analyzed by simulating a numerical solution of the model. This research field is also known as mathematical biology.

**Bioinformatics.** This research domain is the result of the interplay between biologists and computer science scholars. The main aim of this research field is the capture and interpretation of biological data by employing computer software programs and the internet. Agent-based models are also proposed and employed for the analysis and management of data in modern biology and medicine.

An agent-based model is based on the definition of entities (agents), a set of relationships and a framework for simulating agent behaviors and interactions. The reader is addressed to [9] for a deeper understanding of this research field. It is worth stressing that bioinformatics has largely evolved in the last decade and many subfields have been emerged.

**Biomechanics.** This research domain is mainly the outcome of the interplay between biologists and mechanical/biomedical engineers. This research field has recently captured the interest of many mathematicians and physicists. In this research field, the methods of mechanics are employed and in particular the movement and structure of biological systems are modeled and simulated [10]. The main methods employed in biomechanics are continuum mechanics [11], mechanism analysis, structural analysis, kinematics and dynamics. Recently applications of biomechanics refer to sport [12], implant, biomaterials, biofluids. It is worth pointing out that, in the last decade biomechanics has largely increasing its application domain.

**Biophysics.** This research domain is mainly the consequence of the interplay between biologists and physicists/chemists. The methods of physics are employed in biophysics and all scales of biological organization, from molecular to organismic and populations, are covered [13]. In particular

the interactions between the various systems of a cell, including the interactions between DNA, RNA and protein biosynthesis, are of great interest in biophysics. Moreover, molecular biology takes great advantage from the collaboration with physicists which support the physical knowledge behind the biomolecular phenomena. Among the research fields mentioned above, biophysics is considered as the research field that strongly overlaps with the other sciences.

According to the above classification, the interplay among the different scientists working in biomathematics, bioinformatics, biomechanics and biophysics has a key role in order to obtain a complete description of a biological system, namely in the development of a unified method which results in a multiscale approach. Indeed, for instance, the modeling from the molecular to the cellular scale needs the definition of the clustering of genes that produce certain phenomena at the cellular scale.

The development of a multiscale approach requires a linking among the different approaches and methods employed at each scale of observation. In particular the same phenomenon can be modeled by recurring to different approaches at different scales. In many branches of biology, such as molecular and cell biology, microbiology and histology, three mains representations scales are common to complex biological systems: Microscopic scale (molecular: gene expression and signal transduction), mesoscopic scale (cellular: cell movement and extracellular phenomena), and macroscopic scale (tissue: organ function and systemic circulation). However other scales of representation can be proposed considering the length scales of a biological system. It is worth stressing that the same method can be employed to two different scales. Indeed if the interest is the time evolution of a macroscopic quantity of the system, e.g. the density of a cell population, this quantity can be modeled by an ordinary differential equation if the cell population is homogeneous in space or by a partial differential equation if space dynamics needs to be taken into account. Accordingly the proposition of a new observation and/or representation scale or the adaptation of a specific method for the modeling of a specific phenomenon of a complex biological system is the main interest of this special issue.

In the current pertinent literature, the modeling methods developed at each scale can be summarized as follows:

- **microscopic scale** by means of ordinary differential equations, delay differential equations, boolean network modeling, graph theory logical, rule-based models;
- **mesoscopic scale** by means of partial differential equations, age-structured models, stochastic differential equations, reaction–diffusion equations, boolean network modeling, cellular automata, agent-based models, Potts models, lattice gas, lattice Boltzmann, kineti theory;
- **macroscopic scale** by means of ordinary differential equations, partial differential equations, lattice-based models, continuum mechanics, mechano-biological framework, agent-based models, lattice Boltzman.

A multiscale approach consists in linking the modeling frameworks proposed to lower and upper scales. The link can be obtained by introducing into a framework at a specific scale (usually the upper scale) a quantity related to the lower scale or by obtaining the dynamics at a upper scale as limit of the dynamics at lower scale (asymptotic methods). Multiscale approaches have been proposed for the tumor growth [14], would healing diseases [15], immune system [16], neural system [17], tissue engineering [18].

It is worth stressing that each modeling method presents advantages and disadvantages. Indeed the derivation of a specific theoretical model usually need assumptions which can reduce the complexity of the phenomenon and then approximate its analysis and simulation. Moreover some

methods require a high computational analysis and then can be very expensive from the modeling point of view [19,20]. Bearing all above in mind, a multiscale analysis and modeling need a particular attention. Recently the definition of hybrid models, combining the above mentioned different approaches, has gained much attention. An hybrid model helps to resolve the weakness of each approach. This is an important perspective which represents another interest of this special issue.

The multidisciplinary collaboration among scholars of the biological sciences and of the applied sciences should provide the good answers to the multiscale modeling of a complex biological system and the papers published in this special issue can be considered as a primordial contribution to this research field.

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