

Mathematics and Complexity in Biological Sciences

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This special issue continues the tradition of the journal *Mathematical Models and Methods in Applied Sciences* on the modeling, qualitative analysis, and simulation of complex systems. More precisely, systems of many individuals interacting in a non-linear manner. The previous two special issues were dedicated to the more general framework of mathematics applied to the modeling of complex dynamics in life and human sciences ^{2,3}. This special issue specifically focus on biological systems viewed as living, hence complex, systems.

Some general reasonings can be proposed on the specific characteristics of the complexity of biological systems. The following ones have been selected, according to the authors' bias, among various ones:

- 1.** Living entities are capable to develop specific *strategies* and *organization abilities* that depend on the state of the surrounding environment. These can be expressed without the application of any external organizing principle. In general, they typically operate *out-of-equilibrium*. For example, a constant struggle with the environment is developed to remain in a particular out-of-equilibrium state, namely stay alive ¹³.
- 2.** The ability to express a strategy is not the same for all entities, namely *heterogeneity* characterizes a great part of living systems. Namely, the characteristics of interacting entities can even differ from an entity to another belonging to the same structure. In biology, this is due to different phenotype expressions generated by the same genotype. Such strategic ability in various cases evolves in time. In fact, living systems receive inputs from their environments and have the *ability to learn from past experience* to adapt themselves to the environmental conditions ^{18,18}.
- 3.** The study of complex living systems always needs a *multiscale approach*. For instance, the dynamics of a cell at the molecular (genetic) level determines the cellular behaviors. As a matter of fact, the structure of macroscopic tissues depends on such a dynamics. Macroscopic behaviors can be interpreted in a broad sense. For

instance, tissues, populations of vertebrates, organs.

4. Interactions are *nonlinearly additive* and involve immediate neighbors, but in some cases also distant particles. Indeed, living systems have the ability to communicate and can choose different observation paths. In some cases, the topological distribution of a fixed number of neighbors can play a prominent role in the development of the strategy and interactions. Interactions modify their state according to the strategy they develop. Living entities *play a game at each interaction* with an output that is technically related to their strategy often related to surviving and adaptation ability.

5. All living systems are evolutionary. For instance birth processes can generate individuals more fitted to the environment, who in turn generate new individuals again more fitted to the outer environment. Neglecting this aspect means that the time scale of observation and modeling of the system itself is not long enough to observe evolutionary events. Such a time scale can be very short for cellular systems and very long for vertebrates.

Additional technical difficulties are induced by a large number of variables, which are needed to describe their overall state. Therefore, the number of equations needed for the modeling approach may be too large to be practically treated. More precisely, biological systems are different from the physical systems analyzed by statistical mechanics, which typically deals with systems containing many copies of a few interacting components, whereas cells contain from millions to a few copies of each of thousands of different components, each with specific interactions.

It is plain that a system biology approach is needed to reduce the complexity of the overall system. For instance, by splitting it into suitable subsystems, and subsequently by developing mathematical tools suitable to model the specific system under consideration by an approach that retains, as far as possible, the afore-said five key features. In general, the collective overall behavior of large biological systems constituted by several interacting entities, from genes to cells and organs, is determined by the dynamics of their interactions. On the other hand, a traditional modeling of individual dynamics does not lead in a straightforward way to a mathematical description of collective emerging behaviors. Moreover the dynamics of each entity depends on the dynamics at the lower scale

It is plain from the above introductory notes that applied mathematicians look at suitable developments of mathematical methods of statistical physics to model the collective behavior of complex living systems starting from their interactions at the low scales. Therefore, nowadays tools taken from this field are being used by both physicists and mathematicians focusing on the afore-said aim. However, the straightforward application of known methods do not generally lead to satisfactory results. For instance modeling linear interactions is in contrast with recent studies¹, which conjecture, on the basis of empirical data⁷, that some groups of animals develop a common strategy based on interactions depending on topological rather than metric distances. This opens some very interesting avenues in modeling. New

tools have to be developed to model, within a multiscale approach, complex systems constituted by several interacting entities.

After the reasonings that have been given above, the description of the contents of this special issue can be given. It will be specifically referred to the afore mentioned complexity features. Indeed, all papers in this special issue retain some of them, while all papers specifically refer to the third characteristics, namely to the multiscale aspects of biological systems. An additional common issue is that these papers cover the whole path from modeling, after an appropriate phenomenological observation of the system under consideration, to simulation. In some papers the qualitative analysis is developed, prior to simulations, of the good position of the mathematical problems generated by the application of models to the analysis of real biological phenomena.

The paper by Du, Xu, Shrouf, and Alber¹¹ presents a model of swarming of a special biological system, namely the so-called *P. aeruginosa* focusing on the influence of the surrounding environment modelled at the macroscopic scale by film equations and convection-reaction equation, while the modeling at the microscopic scale is delivered by a cell-based stochastic discrete model.

The following two papers presents two different concepts of populations in a different context. The first one by Ducrot, Le Foll, Magal, Murakawa, Pasquer, and Webb¹² models the dynamics of a cell culture in vitro by the approach population dynamics with internal structure²². where the description of the collective dynamics takes into account several features at the microscopic scale. A qualitative analysis and the and simulation that visualize cell clustering phenomena enrich the presentation. The second one by Delitala, Pucci, and Salvatori¹⁰ focus on the modeling of the onset and the spread of epidemics for individuals subject to a virus, which progressively mutates towards malignant states. This paper is the natural development of the approach proposed in⁷ and is based on some recent developments of the so-called kinetic theory for active particles⁴. A detailed qualitative analysis assures the good position of the initial value problem, while various simulations allow the visualization the evolution of the epidemics on the affected individuals contrasted by the immune system.

Different aspects of pattern formation somehow related to morphogenesis and swarming are treated in^{6,7}, and¹¹. In particular, the paper by Cerreti, Perthame, Schmeiser, and Tang⁷ study a development a hyperbolic Keller-Segel model related to swarming phenomena of the bacteria *Bacillus subtilis*. Empirical data show that the cells are able to proliferate and exhibit complex patterns including dendritic ramification. A new class of models is proposed and the afore-said phenomena are related to branching instabilities. Simulations visualize the prediction of the model.

The paper by Calvo, Mazon, Soler, and Verbeni⁶ deals with flux limited equations arising in the transport of morphogeneses and develop a qualitative analysis on various problems such as existence of steady states, propagation of fronts with finite speed. Simulations support the analytic results. The introduction of nonlinear flux limited equations shows to be an interesting method to model complex biological

phenomena, which overcomes the unrealistic descriptions such blow up of solutions.

Finally, the paper by Koumoutsakos, Bayati, Milde, and Tauriello¹⁶ completes the special issue by presenting a computational method that appears to be extremely well suited to develop simulations for complex biological systems in general and for those proposed in this special issue. Computations are based on particle interacting methods¹⁵. Therefore it is appropriate to resolve their hierarchical, spatial and temporal complexity. Possibly ranging from the molecular to the organismal level. The contents focus the simulation of morphogenesis phenomena such as those treated in the afore-cited papers.

Let us finally consider a question, which is quite naturally posed when mathematics is applied to biological sciences focusing on the interplay between the two different disciplines, namely mathematics and biology. More precisely, let us consider the following question posed in⁵ focusing on the general topic of evolution from small living entities, for instance cells, to vertebrates. The question, or dilemma, is as follows: *Should mathematics attempt to reproduce experiments by equations whose parameters are identified on the basis of empirical data, or develop new structures, hopefully a new theory, able to capture the complexity of the biological phenomena and finally to base experiments on theoretical foundations?*

This question witnesses the presence of an intellectual conflict within the scientific community. Although, applied mathematicians are attracted by the second opportunity that aims at developing new mathematical theories and induce them to tackle new challenging problems. This trend should not be considered a naive ambition. In fact, the scientific community is aware that one of the great scientific revolutions of this century is going to be the mathematical formalization of biological sciences as it happened in the past centuries of the successful interplay between mathematics and physics followed by a great impact on technology.

This means that the traditional approach of the research approach to biology, generally based on conjectures and experiments, will be accompanied by the rigorous formalization that the tools of mathematics can offer by a variety of different approaches, from the determinism of differential equations to probability and stochastic games, always related to a multiscale framework, where different methods need to be used at each representation scale.

One of the various difficulties that have to be faced in this ambitious objective is the lack of first principles, which characterize living systems^{17,14,20}. This difficulty and several unsuccessful attempts have contributed to a somehow pessimistic attitude expressed by several authors. On the other hand, this century witnesses not only the presence of optimistic attitudes, such as that offered by Woose²¹, who stimulates the development of new system biology approach, but also by the hints of the Nobel laureate Hartwell¹³, who invites mathematicians and physicists to tackle the complexity of biology viewed as the sciences of living systems.

Based on the above reasonings, we feel confident to state that developing a mathematics for living systems is a great challenge. When this objective is pursued, the above question is not any more a dilemma. In fact, even experiments have to

take into account that they operate in conditions generally close to steady states that differs substantially from those of real living conditions. Hence mathematical methods can contribute to a deeper understanding of experiments designed to capture specific aspects of living systems.

Our hope is that the papers of this issue, can contribute to a deeper understanding of the mathematical strategies to achieve the afore said important objective.

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