

## Foreword to the special issue on “Attempts of a mathematical uprising for restructuring biomedical sciences”

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Mathematical Biology aims to provide a sound mathematical description of biological processes, with the use of tools useful in both theoretical or practical investigations. Reducing to the essential, there are two opposite approaches relevant in building a biomathematical model: either simplifying an inherently complicated biological pattern or being as close as possible to the experimental data. Passing from one extreme to the other, there are a number of different shades which span all of the possible intermediate choices.

A crucial rôle is played by the power of the model of providing reliable forecasts (either qualitative or quantitative) that might not be evident to the experimenter. Viceversa, without any experiment, no model can be capable of giving an evaluable prediction. This is vaguely reminiscent of the ancient folk paradox “Which came first, the chicken or the egg?”, becoming, in the present context, “Which came first, Mathematics or Biology?”. Circumventing the rules, we support the point of view that the best choice is to take advantage of the complementarity of the two disciplines, with both pros and cons on both sides. On the one hand, Mathematics guide the modeling of many biological processes; on the other hand, Biology has contributed to the development of new mathematical techniques. Examples are provided by a variety of population dynamics, ecology, genetics and epidemics taking advantage of deterministic or probabilistic descriptions. Most of the joint work between biologists, physicists, chemists and engineers involve analysis of mathematical structures and its correspondent computational understanding.

Finding the precise origin of Mathematical Biology is a difficult (if not impossible) task. Someone dates it back to ancient Greece, with Pythagoras and Aristotle; others consider that the first mathematician to be interested in biological topics is Leonardo Fibonacci (1170–1242) with the homonymous sequence aiming to describe the dynamics of the number of rabbits. Coming closer to the present days in both time and attitude, in the XIX century, Bernoulli proposed a model for the evolution of smallpox diffusion in a population, leading to a number of subsequent

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population dynamics models proposed by different authors (Malthus, Verhulst, Lotka, Volterra ...).

A turning point in the modern era of Biomathematics dates back to about one century ago, with the publication of D'Arcy Wentworth Thompson's masterpiece *On Growth and Form*, where, in the Prefatory note, it is crystal-clear stated that

*it is not the biologist with an inlinking in mathematics, but the skilled and learned mathematician who must ultimately deal with such problems as are sketched and adumbrated here*

urging mathematicians to contribute to the understanding of biological phenomena. The interest in Biomathematics has increased rapidly since the '60s, due to a number of reasons: the rapid growth of data-rich information sets, resulting from the genomics revolution, difficult to understand without the use of analytical tools; the recent development of mathematical tools (such as *Chaos Theory*) to help understand complex and non-linear mechanisms in Biology; the increase in computing power that facilitates numerical simulations not previously possible; a growing interest in experimentation *in silico* due to ethical considerations related to human and animal research.

More than one century has been passed since the publication of the volume by D'Arcy Wentworth Thompson, and the synergy between Mathematics and Biology has reached nowadays a significant maturity, well-documented by the countless number of joint collaborations and topics involved –spanning from genome sequencing to organisms description– as a consequence of the high-level of heterogeneity inherent in the living world. Fortunately, the best achievements of the exploration has been performed when interdisciplinary approach has been successfully entered into the picture.

The purpose of this Special Issue, output of the corresponding Minisymposium –with the same title and celebrating the ESMTB-EMS Year of Mathematical Biology 2018– that took place during the SIMAI 2018 Conference held in Rome (Italy), is to provide genuine and critical presentations on different aspects concurring to the discussion, with particular attention to the definition of a rigorous language appropriate for biological phenomena and useful for medical applications. We aim at giving the opportunity for a truly interdisciplinary exchange of the research outcome in the field of systems biology from epistemology to experimental medicine, passing through applied mathematics, bio-statistics and scientific computing.

The papers composing this Special Issue address some of the before mentioned themes and are a first attempt to drive the reader attention on them.

To begin with, Giuliani invite us to reflect on the need of *re-thinking the quantitative approach to Biology* since there are two basic inconsistencies of the mathematical and physical way of reasoning when dealing with biology: too abstract solutions and too ideal cases to approximate real world. He tries to isolate the roots of the problem and sketch some possible solutions encouraging mathematicians to take interest in the real biological content of the models under investigation.

In this context, Montevil warns us that the emergence of *mathematical modelling in Life Science* could be both a chance and a danger for biological knowledge. Indeed, such kind of modelling is often not performed by biologists themselves, but by mathematicians, computer scientists and/or physicists. Their works bring new concepts in Biology, but these tools and theoretical frameworks were not designed to accommodate the specificities of life and living organisms, and the bioscientists involved are not always knowledgeable of these strengths. Even though each of these approaches has its merits and successes, the author thinks that they should be embedded in a more profound theoretical framework based on biological principles. In his paper, he presents several theoretical ideas which are the result of a *trans-disciplinary effort* towards a theory of organisms. Also, he provides an overview of the concepts which follow from the analysis of these ideas, and illustrates some of them with a mathematical plan for allometric relations in biology.

In light of the above considerations and remarks, the remaining part of the volume collects examples of biological phenomena and corresponding mathematical tools that have been properly adapted to them: namely, wave-like behaviours, tumour growth models, cerebrospinal fluid dynamics.

One important class of problems in Mathematical Biology consists in the identification, modelling, and simulation of systems that exhibit invasion phenomena of one state into another, as observed in embryonic development, population dynamics, wound healing and epidemiology. Probably, the most ancient mathematical model that admits a rigid profile, translating with constant speed, is the Fisher's equation, also known as Fisher-KPP model. In their paper, Martinson, Byrne and Maini point out that investigating *traveling wave solutions* with pulled fronts presents a challenge for researchers since in many biological applications the local dynamics near the wave front may not necessarily be appropriately modelled by an evolutive partial differential equation. In this respect, they review *multiscale approaches* to simulate systems with wave-like behaviour, focusing on the paradigm example of Fisher's equation and finally, discuss a potential application of these algorithms in the context of cancer biology, providing an overview of different approaches that can be of interest for biomathematicians.

Concerning tumour growth models, Padilla and Plaza deal with the so-called *tumour growth paradox* which refers to the fact that, by clinical observation, some incomplete cancer treatments may enhance tumour growth. Much probably, this is mainly due to the presence of *cancer stem cells* (CSCs), which have been identified in many types of cancer such as leukaemia and carcinomas of breast, colon, brain and pancreas, among others. In their paper, the authors review some recent mathematical models based on the CSCs hypothesis and proposed to account such (apparent) inconsistency. When diffusion effects are neglected, the resulting purely dynamical system underlies a sort of tumour growth paradoxical behaviour as a result of the immune response from cytotoxic treatments. Subsequently, it is discussed the possible effects of adding diffusion on such growth behaviour into the original framework by applying the *invariant foliation theory*.

In their contribution, Pera and collaborators introduce us on the importance of

*parallel computing methods* applied in tumour models simulations. Mathematical models for tumour invasion are often used to predict the behaviour of cancer evolution; therefore, their numerical solution often requires high spatial resolution to capture detailed biophysical phenomena. As a consequence, long computational times are demanded when using a serial implementation of numerical schemes. Parallel computing can improve dramatically the time efficiency of some of such numerical methods –such as finite differences algorithms– which are relatively simple to implement and apply to tumour invasion models. For clinical operators and applied scientists involved in setting up realistic experiments, the possibility of running fast comparative simulations using simple algorithms implemented into affordable processors is of primary interest, and that is where the use of *Graphical Processing Units* (GPUs) excel. In their paper, the authors focus on a mathematical model of anisotropic and heterogeneous diffusion of tumour cells, modelled by a set of time-evolution parabolic equations. The codes used in this work are designed using *CUDA platform* (Compute Unified Device Architecture NVIDIA 2007), which was designed to support GPU execution of programs and focuses on data parallelism.

Next, Moschetta and Simeoni deal with the so-called *Gatenby-Gawlinski model* for the description of cancer invasion. By starting from the results available in the literature, they contribute –mainly through a numerical approach– to the understanding of the dynamics the mathematical model. The specific form of the diffusive term within the ill tissue equation is suitably assembled to properly reproduce the main principle –usually known as the *Warburg effect*– the real phenomena is based on. Simulations are performed and realistic evidence emerging from the experiments is highlighted, including the proposal of an appropriate system reduction which could be useful to keep the basic qualitative features of the model with a diminished number of unknown. Specific reference is made to the analysis of the so-called *tumour-host gap* with many numerical simulations –performed also in higher dimensions– trying to catch the presence of such an interstitial space.

Finally, the Special Issue ends with an example of mathematical models for biofluids. Romagnoli investigates models for the *cerebrospinal fluid (CSF) dynamics*. The main difficulty in analyzing the intracranial dynamics is represented by the particular structure of the human brain that includes very complex elements. Specifically, this physiological body fluid shows a pulsating movement within the ventricular system and between the cranial vault and spinal compartments. Recent efforts in scientific and clinical communities are aimed precisely at quantifying the critical parameters relating to normal intracranial dynamics and at identifying the deviations characterized by eventual diseases. Quantitative models are fundamental to support new intuitions about the cerebrospinal fluid in the central nervous system. In this scenario, the pivotal role of mathematical models is evident being able to achieve a better interpretation about *in vivo* data detected at multiple length scales and anatomical positions inside the intracranial pattern. In such a framework, Romagnoli investigates the mathematics which is the starting point of the CSF dynamics modelization and presents an overview of numerical simulations

aimed at confirming and completing the theoretical results. The computational results are discussed from a qualitative standpoint and when available compared with quantitative information derived from literature or experimental data.

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