

PREFACE

This special issue is the second of three issues of this journal devoted to cancer modelling with special emphasis on innovative mathematical methods developed to describe, by mathematical equations, the dynamics of cancer growth. It aims to provide a forum for applied mathematicians involved in the field to present a range of mathematical approaches and discuss the interplay between them. We hope that this will lead to the generation of new mathematical tools that will be necessary if significant progress is to be made in this ambitious objective.

In the industrial nations, cancer has now moved from seventh to second place in the league table of fatal diseases, being surpassed only by cardiovascular diseases. Indeed, the World Health Organization estimates that at present cancer kills approximately six million people annually. Furthermore, as the European population ages (in the near future there will be more people in Europe over 60 than under 20), age-related illnesses such as cancer and diabetes will become even more of a problem. For these reasons the fight against cancer is of major importance for public health (and also economic resources) throughout the world.

Before dealing with the specific topics covered in this issue, it is worth mentioning some general aspects concerning the interaction between mathematics and the biological sciences. In particular, May¹ addresses this in an interesting paper which looks for a balance between a naive enthusiastic attitude and unreasonable scepticism. It brings to our attention a crucial observation:

- *In the physical sciences, mathematical theory and experimental investigation have always marched together. Mathematics has been less intrusive in the life sciences, possibly because they have been until recently descriptive, lacking the invariance principles and fundamental natural constants of physics.*

Moreover, the same author reports a sentence from the great Charles Darwin:

- *I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics; for men thus endowed seem to have an extra sense.*

Problems specific to interdisciplinary approaches are discussed in various papers authored by scientists in the field of molecular and cellular biology. The paper by Hartwell *et al.*² analyzes the conceptual differences and difficulties between dealing with inert and living matter: living systems are characterized by specific features

absent in classical mechanics, such as reproduction, competition, cell cycle, ability to interact with other entities and to generate dynamics more complex than those emerging from Newtonian mechanics. Essentially analogous concepts are proposed in the paper by Reed³ from the viewpoint of applied mathematicians.

Modelling and simulation of tumor growth in competition with the immune system is certainly one of the challenging frontiers of applied mathematics which may well have a great impact both on the quality of life, and development of the mathematical sciences. It is true that mathematics cannot fully solve problems in immunology and medicine. However, applied mathematics may be able to provide a framework in which experimental results can be interpreted, and a quantitative analysis of external actions to control neoplastic growth can be developed. Specifically, models and simulations of particular behaviors of immune system-tumor competition can reduce the amount of experimentation necessary for drug and therapy development. Moreover, the mathematical theory developed might not only provide a detailed description of the spatiotemporal evolution of the system, but also may help us understand and manipulate aspects of the process that are difficult to access experimentally.

One of the unifying underlying challenges proposed in the papers published in the first issue was the mathematical understanding of the multiscale nature of cancer. Indeed, the preface to that issue⁴ provides a description of the various phenomena at the three natural spatial scales, subcellular, cellular and macroscopic, and discusses how different mathematical tools need to be developed at each scale.

The first issue is characterized by an interesting conceptual link joining some of the papers published in the issue. For instance, a general framework towards the modelling of multicellular systems is proposed in Ref. 5, while the asymptotic theory proposed in Ref. 6 shows that the macroscopic model proposed in Ref. 7 is consistent with microscopic models of the type proposed in Ref. 5.

The above results, however, do not provide a full answer to the mathematical problem of deriving macroscopic equations from the underlying microscopic equations. Indeed, biological functions evolve in time,^{8,9} so that, for example, the equations describing the tissue mechanics may change in type as documented in Ref. 10 to reflect changes in mechanical properties. In addition, macroscopic approaches need to carefully take into account the geometrical detail of biological structures at both the micro- and macro-scopic levels.^{11,12}

Clearly, there are a great variety of challenging mathematical problems related to cancer modelling open to future research activity and this strongly motivates the effort to build a bridge between mathematics and biology. Moreover, applied mathematicians are attracted by the challenge of the remarkable difficulty of several open analytic problems: Four specific problems of this sort can be selected with direct reference to the specific contents of this issue.

- (i) What is the correct mathematical framework to deal with multicellular systems? Does this have a unique answer?

- (ii) Which type of macroscopic phenomena can be accurately described by models at the multicellular scale?
- (iii) Supposing that the above problems are technically solved, is this sufficient to describe the overall system, or, is it necessary to consider the problem as composed of a series of interacting sub-systems, each operating at a specific scale?
- (iv) Is the selection of one scale only sufficient to model the behavior of each sub-system, or, even at this level, is it necessary to consider more than one scale?

The above issues generate interesting and challenging mathematical problems. Their analysis may not, in some cases, have an immediate impact on biology. This is an additional aspect of the interplay between mathematics and biology: in this case biologists may be disappointed by the fatal attraction of mathematicians towards challenging mathematical problems, even when the impact to applications is not evident. On the other hand, mathematicians should not be blamed: at least in some cases, this analysis leads to results which are useful for various different fields of applied sciences, hopefully also to the progress of the mathematical sciences. In this respect, mathematicians are no different from the biologists who become engrossed in technical experimental detail and lose sight of the overall goal.

Indeed, one may argue that it is essential for researchers in each discipline to do exactly that, while it is the responsibility (and the art) of interdisciplinary research to see how different techniques from different disciplines may be used to answer the overarching scientific questions.

This special issue presents six research papers which deal with different aspects of the mathematical problems which have been outlined above. While these papers do not provide a final answer to the above complex issues, they formulate many of the crucial questions and make significant progress in answering them, either by providing experimentally testable predictions, or by developing a mathematical modelling framework which may allow us to build more biologically realistic models.

Specific results towards developing mathematical models of the immune competition at the cellular level are given by the first paper of this issue by Lollini, Motta and Pappalardo,¹³ which is the output of the collaboration among experts in the field of mathematics, informatics, and immunology. The paper develops an analysis based on the modelling by a computational scheme of the interactions among tumor cells in competition with engineered immune cells trained to identify the aggressive host. The analysis is developed in the context of the results of an *in vitro* experiment, which shows how the model is able to follow the empirical data obtained by the experiment. It is an interesting approach which could help to inform how analytic models should be developed, referred to recent theories on immune competition.^{14,15}

An alternative mathematical approach is developed within the framework of competing population dynamics for multicellular systems assuming that cells have an internal state which may evolve in time and generate biological processes. If

such a state is the same for all populations, then the model is stated in terms of partial differential equations, where the microscopic state is regarded as an internal structure. The paper by Michel¹⁶ is proposed within the above framework. In detail, the paper analyzes the dynamics of cell division as a fragmentation process which preserves the total mass. Actually the paper is focussed on analytic issues: the qualitative analysis leads to a proof of the existence of solutions obtained as a sum of an explicit series. This paper shows, in particular, that applied mathematicians are attracted by analytic problems posed by the application of models to the analysis of real biological phenomena.

As documented in the first special issue,^{5,6} the microscopic state can be distributed over a cell population so that the dependent variable is a suitable probability distribution. The paper by Kheifetz, Kogan, and Agur,¹⁷ analyzes a model of a cell population with a distributed cell-cycle duration which predicts long time evolution under the action of chemotherapy. The paper develops both analytic and computational issues carefully related to the interpretation of biological phenomena related to the application of specific therapies.

The paper by Chalub, Dolak-Struss, Markowich, Oeltz, Schmeiser, and Sorel¹⁸ operates in a mathematically analogous framework, where now the cell distribution is in space. Specifically, this paper analyzes cell motion coupled to a diffusion equation for chemoattractants, and shows how macroscopic models of the cell-chemoattractant phenomena can be derived from the underlying kinetic description. This paper is also a useful reference for the mathematical literature in this field, as well as providing possible avenues to further understanding of cell-chemotaxis processes in cancer dynamics.

As already mentioned, the analysis of models of specific phenomena or sub-systems (of the overall system constituted by a solid tumor interacting with the environment) should be properly considered in the context of the whole system. An analysis of this type is proposed in the paper by Bru and Herrero,¹⁹ which investigates the role of phenomena at the cellular scale on the evolution of the macroscopic system. It is a problem of two interacting scales which has a relevant biological impact. This paper considers carefully the physical interpretation of the above complex interplay and how to translate such a reasoning into mathematical equations.

Finally, the paper by Byrne, Owen, Alarcon, Murphy, and Maini,²⁰ deals with the challenge of multiscale modelling by considering the behavior of the whole system as emerging from the interaction of coupled subsystems represented by models operating at specific length scales. This paper makes experimentally testable predictions as well as raising a number of open mathematical questions such as, for example, proving the robustness and range of applicability of such an approach.

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