Preface

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This special issue is devoted to cancer modelling, with emphasis on multiscale methods to describe the complex biological phenomena related to the onset of tumour cells due to genetic mutations and their proliferation, uncontested by the immune system or by specific therapeutic intervention. It is an important and challenging research field which attracts an increasing number of applied mathematicians involved in a research field which Gatenby and Maini [12] aptly designated “*Mathematical Oncology*”.

The interest of applied mathematicians in the above research field is prompted by both social as well as mathematical considerations. In the first place, cancer is one of the most destructive diseases in the industrialised nations, being surpassed only by cardiovascular diseases. Indeed, the World Health Organisation estimates that, at present, cancer kills approximately six million people annually. For this reason, the fight against cancer is of major importance to public health (and also economic resources) throughout the world. In addition, one of the great scientific revolutions of this century is undoubtedly going to be the mathematical formalisation of phenomena occurring in the life sciences and medicine, much as the mathematics has revolutionised the physical sciences over the past two centuries.

These motivations are reason enough to explain why applied mathematicians are becoming increasingly involved in the field of mathematical oncology and contributing to the understanding of the complexities of cancer. It is not an easy task and many fundamental conceptual issues need to be resolved. Indeed Bellomo and Maini [4,5] raise the following important questions:

What is the correct mathematical framework to deal with multicellular systems? Does this question have a unique answer? Is the selection of one scale only sufficient to model the system or is it necessary to consider more than one scale?

Which is the relevant biological phenomena and which is the scale corresponding to each of them? For example what is the scale suitable to represent conceivable therapeutic actions?

Suppose the above questions are technically solved, is it necessary to consider the problem as composed of a series of interacting sub-systems, each operating at a specific scale?

These questions may be addressed in the following:

- (i) The mathematical description should take into account the essential features of the biological system and develop a mathematical formalism appropriate to the biology under investigation.
- (ii) The resulting system will be complex and characterized by several subsystems each of which will involve phenomena at different spatial

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and/or time scales. Their interaction provides the evolution of the overall system.

Regarding the first aspect, it is worth drawing attention to some remarks of Hartwell *et al.* [16]:

Biological systems are very different from the physical or chemical systems analyzed by statistical mechanics or hydrodynamics. Statistical mechanics typically deals with systems containing many copies of a few interacting components, whereas cells contain from millions to a few copies of thousands of different components, each with very specific interactions.

Although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiate biology from other natural sciences. More important, what really distinguish biology from physics are survival and reproduction, and the concomitant notion of function.

Further, it is worth stressing that analogous concepts, although with a different expository style, are addressed to the applied mathematical community by May [20] and Reed [23].

One of the unifying underlying challenges proposed in the papers in this issue is the modelling and simulation of therapeutical actions possibly related to empirical data and medical strategies. These issues are relevant to and within the aims of the journal. Most of the papers involve the three natural spatial scales, subcellular, cellular and macroscopic and show how different mathematical tools need to be developed at each scale. Nevertheless, the role of the models is not simply limited to the interpretation of empirical data or simulations of specific phenomena already understood in medicine and biology. The modelling ideas may hopefully shed light on phenomena not easily examined by exiting experiments. Indeed, the models may suggest novel experimentation which respects the stochastic and unpredictable nature of cancer as evidenced by Gillet [14].

The multiscale nature of cancer is well presented in the paper by Alarcón *et al.* [2] which deals with the challenge of modelling tumour vasculogenesis and chemotherapy via the interaction of coupled subsystems operating on different length scales. This paper is based on the multiscale approach initiated by Alarcón *et al.* [1]. Specific aspects and the need for a multiscale approach was anticipated by Levine *et al.* [18] in relation to the specific problem of capillary formation initiating angiogenesis.

The subject of the above paper is a valuable reference to the paper of Pitt-Francis *et al.* [21] written with experimentalists in mind by indicating interactions between experiment, modelling and simulations. The paper deals with imaging techniques applied to the analysis of colorectal cancer at different observational scales.

The analysis of the papers which follow is mainly focussed on the modelling and simulations of specific therapeutic strategies. For example the paper by Dawson and Hillen [11] analyzes cell cycle models in the control of tumour growth using radiation treatment. An interesting research perspective is offered by Gatenby *et al.* [13] who employ evolutionary and game theory to model carcinogenesis.

The early stage of tumour growth in competition with the immune system, including activation of the immune response, is examined in the paper by Brazzoli and Chauviere [6] which shows how activation of the immune response may modify its function in competition with tumour cells. This paper makes reference to the biological theory of progression [15] and to the mathematical kinetic theory of active particles critically analyzed by Bellomo and Forni [3].

The paper by Marciniak-Czochra and Kimmel [19] is also devoted to the analysis of the early stages of tumour growth with special attention to the dynamics generated by signalling along linear and surface structures. This paper has the merit of linking models at the cellular and subcellular scale to macroscopic growth phenomena. This is an interesting topic as evidenced, among others, by the work of Bru *et al.* [7]. For mathematical aspects, we refer to Capasso and Micheletti [8], who consider modelling surface phenomena and Chaplain and Lolas [9], who discuss spatio-temporal heterogenous phenomena.

The paper by de Pillis *et al.* [10], deals with the analysis of the immune response based on the interpretation of empirical data provided by medicine. The analysis is developed at the macroscopic scale after a detailed analysis of the existing literature on models proposed at different scales as discussed in the monograph edited by Preziosi [22]. An interesting example of the interaction between mathematics and medicine is the paper by Kheiffetz *et al.* [17], devoted to super-macroscopic modelling of fluid retention side effects on chemotherapy supportive treatment. The mathematical modelling is carefully correlated to data availability and so offers a precise link with the medical sciences.

In conclusion, this issue has been essentially devoted to the interaction between mathematics and medicine. The ultimate goal in the clinical setting is to use mathematical models to help design therapeutic strategies and to optimize them. On the other hand, it needs to be taken into account that applied mathematicians are attracted by the challenges of the remarkable difficulty of several open analytic problems even though their analysis may not, in some cases, have an immediate impact on biology. Nevertheless, the analysis will lead to results, which are useful to a variety of different fields of the applied sciences as well as the mathematical sciences in general. Furthermore, conceptual mathematical analysis may contribute to the progress of the biological sciences. It is an exciting challenge for the future to work towards a convergence of the experimental approach, the traditional investigative method in the biological sciences, with mathematical modelling and analysis in order to gain a deeper conceptual understanding of the highly non-linear nature of biology.

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