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PREFACE

The scientific community is becoming increasingly aware that the great revolution of this century is going to be the mathematical formalization of phenomena occurring in the Life Sciences, much as the revolution of the past two centuries was the development of the above approach in the Physical Sciences. To quote J. E. Cohen: "Mathematics is Biology's next microscope, only better; Biology is Mathematics' next Physics, only better." This endeavor will be a huge challenge that will require the intellectual energy of scientists working in the field of mathematics and physics collaborating closely with biologists and clinicians. This essentially means that the heuristic experimental approach, which is the traditional investigative method in the Biological Sciences, should be complemented by the mathematical modelling approach. The latter can be used as a hypothesis-testing and indeed, hypothesis-generating, tool which can help to direct experimental research. In turn, the results of experiments help to refine the modelling. The goal of this research is that, by iterating back and forth between experiment and theory, we eventually arrive at a deeper conceptual understanding of how the highly nonlinear processes in biology interact. The ultimate goal in the clinical setting is to use mathematical models to help design therapeutic strategies.

There has, recently, been a significant shift in biological research, with experimentalists now beginning to voice the need for multi-disciplinary research encompassing mathematical and computational approaches. For example, Hartwell et al.[1] and Greller et al.,[2] encourage applied mathematicians to develop mathematical approaches to mathematical modelling of complex systems in molecular biology. These papers, only two amongst several others in a similar vein, not only encourage research activity, but also suggest methodological approaches. Specifically, the first paper provides interesting suggestions towards the mathematical formalization of the *"theory of moduli"*, while the second paper motivates the development of methods of non-equilibrium statistical mechanics to cancer modelling.

Modelling and simulation of tumor growth in competition with the immune system is certainly one of the challenging frontiers of applied mathematics which could have a great impact both on the quality of life and the development of mathematical sciences. It is true that mathematics cannot solve problems of 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 may also help us in understanding and manipulating aspects of the process that are difficult to access experimentally.

The interest of mathematicians in the above field is rapidly growing and is clearly evident in the vast literature appearing in journals of applied mathematics. The state of the art is reported in edited books, e.g. Refs. 3 and 4, where contributions from applied mathematicians to the above-mentioned topics are presented. The interest of applied mathematicians, and the need for developing mathematical approaches motivates, as suggested by Gatenby and Maini,[5] a new branch of mathematical research which may be called "*mathematical oncology*".

One of the major problems in modelling biological systems is the multiscale nature of most biological systems. Hence in a more general setting, the modelling of the tumor-immune system interaction serves as a paradigm that may have more widespread significance. Specifically, the characterization of the system suggests the identification of three *natural scales* which are also connected to different stages of the disease: processes on the *cellular scale* are triggered by signals stemming from the *sub-cellular level* and have an impact on the *macroscopic scale*, i.e. on the organism, as tumor cells condense and when tumors grow and spread. In detail:

The sub-cellular scale: The evolution of a cell is regulated by the genes contained in its nucleus. Receptors on the cell surface can receive signals which are then transmitted to the cell nucleus, where the afore-mentioned genes can be activated or suppressed. In extreme situations, particular signals can induce a cell to reproduce itself in the form of identical descendants — so-called clonal expansion, or to die and disappear apparently without trace — so-called apoptosis or programmed cell death. Clonal expansion activates a competitive-cooperative interaction between tumor cells and cells of the immune system. If the immune system is active and able to recognize the tumor cells, then it may be able to develop a destruction mechanism; otherwise, tumor growth may develop progressively. The activation and deactivation of immune cells, too, can be regulated by cytokine signals.

The cellular scale: On the cellular level, models are proposed to simulate the effects of the failure of programmed cell death and of the loss of cell differentiation. If and when a tumor cell is recognized by immune cells a competition starts which may end up either with the destruction of tumor cells or with the inhibition and depression of the immune system. Cellular interactions are regulated by signals emitted and received by cells through complex reception and transduction processes. Therefore,

the connection to the afore-mentioned sub-cellular scale is evident. On the other hand, the development of tumor cells, if not suppressed by the immune system, tends towards condensation into a solid form so that macroscopic features become important.

The macroscopic scale: After a suitable maturation time, tumor cells may start to condense and aggregate into an entity which eventually evolves as a "quasi-fractal surface" which interacts with the outer environment, for example normal host cells and the immune system. These interactions usually occur on the surface and within a layer where angiogenesis (the process of formation of new blood vessels, induced by factors secreted by the tumor, and vital for tumor growth) takes place. Here, one has the overlap of phenomena at the cellular level with typical macroscopic behavior such as diffusion or, more generally, phenomena that can be related to the mass balance or evolution of macroscopic variables such as tumor size. In a later stage, the tumor can be characterized by *three zones*: in an external layer environmental cells penetrate and determine the detachment of tumor cells; an intermediate layer in which there are clusters of quiescent tumor cells; and an inner zone, which contains necrotic cells. Due to the heterogeneous nature of tumors, some of these "layers" may actually occur as "islands".

Different mathematical methods and structures correspond to the above scales. For instance models at the cellular scale are generally developed in terms of ordinary differential equations or Boolean networks, while multicellular systems are modelled by nonlinear integro-differential equations similar to those of nonlinear kinetic theory (the Boltzmann equation), or by individual-based models which give rise to a large set of discrete equations. Macroscopic models lead to moving boundary problems for systems of nonlinear partial differential equations. Nonlinearity is an intrinsic feature of all models. In short, this system leads to problems that span the breadth of applied mathematics and stretch our computational resources.

From the mathematical viewpoint, the main objective of the series of special issues of which this is the first, is to bring to the attention of the wider mathematical community, the problems involved in multiscale modelling and the methods being presently applied to the analysis of complex biological systems constituted by large systems of interacting cell populations. The following topics can be regarded as new frontiers of applied mathematics:

(i) Modelling and qualitative analysis of systems of nonlinear integro-differential equations related to the mesoscopic (kinetic) description of multicellular systems.[6] The above equations define the evolution over the microscopic state of the cells and includes both mechanical and biological variables. The structure of the equation is somehow analogous to that of mathematical kinetic theory. The substantial difference (and difficulty) is that the dynamics at the cellular scale has to be modelled taking into account the interaction between mechanics and biology.

(ii) Mathematical asymptotic theory suitable to recover the macroscopic description of cell mixtures from the mesoscopic description. The theory should provide a rigorous derivation, rather than a purely phenomenological one, of the mechanics of the systems in terms of partial differential equations, generally nonlinear, of parabolic and hyperbolic type.[7]

(iii) Qualitative and computational analysis of initial-boundary value problems with moving boundary, related to the dynamics of solid tumors described by models derived according to items (i) and (ii).

(iv) Multiscale modelling where a combination of several different mathematical approaches appear, following the conceptual lines given in Refs. 8 and 9, in the formalized description of the whole system.

In general, simulations may need the use of dedicated computer devices, to solve systems which include biological variables in the various transport phenomena related to biological systems.[10] The common feature of the above mathematical approach is that the equations model living matter, and the ability of cells to organize their dynamics needs to be an essential feature of these mathematical models. Another key feature is the multiscale approach to modelling and simulation.[8,9] Indeed, we are convinced that the complexity of the system related to these special issues requires the invention of new mathematical methods, or at least new ideas, to place into a mathematical context the above mentioned complexity.

This special issue presents six research papers which deal with different aspects of the mathematical problems which have been outlined above.

The first paper, by Gatenby, Vincent and Gillies,[11] deals with modelling at the sub-cellular scale with specific focus on an evolutionary game theory approach to somatic evolution to describe how genomic changes result in cancerous cells that can invade normal tissue.

The second paper, by Bellouquid and Delitala,[12] develops methods of mathematical kinetic theory to deal with large systems of active particles, cells whose microscopic state, in addition to a geometrical and mechanical description, also includes biological functions.

Approaches from generalized kinetic theory form a framework in which models of continuum mechanics for biological tissues can be derived and a suitable asymptotic theory, ideally analogous to the one known for classical particles, developed. This mathematical approach is proposed in the third paper, by Lachowicz,[13] where it is shown how the continuous model used in the paper by Chaplain and Lolas[14] can be obtained. The latter paper, the fourth in this issue, presents a variety of interesting phenomena, in the context of cancer invasion of tissues. It is worth pointing out the conceptual connection between the above two papers where the macroscopic description is related to the underlying microscopic description.

The fifth paper, by Bertuzzi, Fasano and Gandolfi,[15] deals with the macroscopic description, and specifically with mathematical aspects of moving boundary problems, for tumor cords incorporating the flow of interstial fluids. Finally, the paper by Hatzikirou, Deutsch, Schaller, Simon and Swanson[16] provides a review, and a critical analysis, of the vast literature concerning mathematical modelling and medical therapies of glioblastoma.

This issue is the first of a series which aims to create a forum for applied mathematicians involved in the field. Hopefully, the interplay between different approaches will lead to the generation of a new mathematics needed to deal with the above class of biological systems and phenomena.

This issue is dedicated to the memory of Lee A. Segel, an applied mathematician who brought mathematics to several areas of the life sciences. His work is an inspiration to us.

References

1. H. L. Hartwell, J. J. Hopfield, S. Leibner and A. W. Murray, From molecular to modular cell biology, *Nature* **402** (1999) c47–c52.
2. L. Greller, F. Tobin and G. Poste, Tumor hetereogenity and progression: Conceptual foundation for modeling, *Inv. Metastasis* **16** (1996) 177–208.
3. Eds. J. Adam and N. Bellomo, *A Survey of Models on Tumor Immune Systems Dynamics* (Birkhäuser, 1997).
4. L. Preziosi, *Modeling Cancer Growth* (CRC Press, 2003).
5. R. A. Gatenby and P. K. Maini, Mathematical oncology: Cancer summed up, *Nature* **421** (2003) 321–323.
6. N. Bellomo, A. Bellouquid and M. Delitala, Mathematical topics in the modelling complex multicellular systems and tumor immune cells competition, *Math. Mod. Meth. Appl. Sci.* **14** (2004) 1683–1733.
7. N. Bellomo and A. Bellouquid, From a class of kinetic models to macroscopic equations for multicellular systems in biology, *Cont. Disc. Dyn. Syst. B* **4** (2004) 59–80.
8. T. Alarcón, H. M. Byrne and P. K. Maini, A mathematical model of the effects of hypoxia on the cell-cycle of normal cancer cells, *J. Theor. Biol.* **229** (2004) 395–411.
9. T. Alarcón, H. M. Byrne and P. K. Maini, A multiple scale model for tumour growth, *SIAM J. Multiscale Simu.* **3** (2005) 440–475.
10. A. Deutsch and S. Dorfman, *Cellular Automaton Modelling of Biological Pattern Formation* (Birkhäuser, 2004).
11. R. A. Gatemby, T. L. Vincent and R. J. Gillies, Evolutionary dynamics in carcinogenesis, *Math. Mod. Meth. Appl. Sci.* **15** (2005) 1619–1638.
12. A. Bellouquid and M. Delitala, Mathematical methods and tools of kinetic theory towards modelling complex biological systems, *Math. Mod. Meth. Appl. Sci.* **15** (2005) 1639–1666.
13. M. Lachowicz, Micro and meso scales of description corresponding to a model of tissue invasion by solid tumors, *Math. Mod. Meth. Appl. Sci.* **15** (2005) 1667–1683.
14. M. A. J. Chaplain and G. Lolas, Mathematical modelling of cancer cell invasion of tissue: The role of the urokinase plasminogen activation system, *Math. Mod. Meth. Appl. Sci.* **15** (2005) 1685–1734.

15. A. Bertuzzi, A. Fasano and A. Gandolfi, A mathematical model for tumor cords incorporating the flow of interstitial fluids, *Math. Mod. Meth. Appl. Sci.* **15** (2005) 1735–1777.
16. H. Hatzikirou, A. Deutsch, C. Schaller, M. Simon and K. Swanson, Mathematical modelling of glioblastoma tumour development: A review, *Math. Mod. Meth. Appl. Sci.* **15** (2005) 1779–1794.

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