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PREFACE

CHALLENGING MATHEMATICAL PROBLEMS IN CANCER MODELLING

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This issue, the third (and final) of a series in this journal devoted to cancer modeling, is focused on analytic problems arising from the application of mathematical models to the simulation of biological phenomena. The contents of the preceding issues are described in the Prefaces.[7,8]

In some cases, the qualitative and computational analyses of problems need the development of sophisticated mathematical methods and even new tools suitable to deal with the complexity inherent to the biological sciences. In particular, cancer modeling generates challenging problems which strongly attract applied mathematicians.

Although the impact of mathematical models on the biological sciences is only now beginning to be evident, the benefits to mathematics of the need to meet the challenge of the novel problems raised by biological systems have been apparent for some time now and we expect that there will be future exciting developments in the mathematical sciences.

This issue presents six research papers which deal with different aspects of mathematical problems related to cancer modelling. They follow from the preceding special issues by focusing on how the modelling approaches have generated specific mathematical problems which will enrich applied mathematics. Moreover, they cover the multiscale aspects of the biological system under consideration, from the microscopic level of genes to the macroscopic level of tissues.

The first paper by Komarova[20] deals with the development of stochastic game methods to model the dynamics of cancer initiation and progression. Possible ways to develop a mathematical approach to describe these highly complex biological phenomena are well documented in the literature in the field of biological sciences.[26,29]

The interest of applied mathematicians in the above topic is ongoing as documented in the papers of the first issue[16,23] focused on the perspective objective of developing a mathematical theory for multicellular systems.[4] The paper by Komarova[20] contributes to the above aim which needs, as an essential step, a deep understanding of the links between the molecular and the cellular scales focused on the mechanisms of genetic mutations that generate the evolution of cellular functions.[17]

The second paper by Bellomo, Bellouquid, Nieto, and Soler[2] deals with the derivation, by asymptotic methods, of macroscopic equations, at the tissue level, from the underlying microscopic (cellular) description.[3] This paper develops a hyperbolic scaling which generates models with source terms related to mutations and proliferation rates. This topic was also dealt with in previous issues looking for diffusion limit methods[22,11] and is a crucial step towards multiscale modeling by identifying the correct mathematical description of living tissues, rather than the heuristic approach of continuum mechanics in which the equations is generally postulated *a priori*. This literature shows that different mathematical structures correspond to different scalings, and that during the time evolution of cancer tissues the structure of the equations also evolves in time due to genetic mutations.[17,29]

Real biological systems are such that even when cells are condensed into solid forms cellular and molecular phenomena still play a crucial role.[10,12,6] This aspect is carefully dealt with in the paper by Marchiniak-Cozchra and Kimmel,[24] which refers to the modeling of the early stage of tumors related to genetic mutations. The model consists of a hybrid system of ordinary and partial differential equations where cell populations develop mutualistic interactions that produce growth factors.

The fourth and fifth papers refer to different aspects of the qualitative analysis of moving boundary problems related to cancer modeling. This is a challenging problem that was also mentioned in the first issue.[5] Specifically, the paper by Wilson, King and Byrne[30] deals with the qualitative analysis and simulations of a moving boundary problem for a two-scale system where biological tissues are in contact with dispersed cells. Therefore, the model operates at the cellular and macroscopic scales. Several important phenomena are related to these types of interactions (free cells with tissue) as documented, in a different context, in the papers by Bru and co-workers.[10,6]

The paper by Friedman[14] deals with the qualitative analysis of moving boundary problems in the context of tumor growth. The novelty of the challenging problems posed and analyzed by Friedman is the study of models where the material behavior of biological tissues changes in type due to genetic mutations. This paper provides applied mathematicians with new research perspectives in a field in which interesting contributions have already been given by Friedman and co-workers,[13] as well as in the first issue of this series devoted to cancer modeling.[5]

The paper by Kim, Stolarska, and Othmer[21] deals with a multiscale approach to modeling avascular tumors. The modeling approach looks at the behavior of the whole as emerging from the interaction of coupled subsystems represented by models operating at specific length scales. The model is focused on the avascular stage. The research line on multiscale modeling was initiated by Alarcon, Byrne and Maini,[13] focused on vascularized tumors, and then developed in a sequel of papers as documented in the bibliography of a paper published in the second issue.[9] It is worth stressing that one of the objectives pursued in Ref. 21 refers to the design of experimentally testable models.

All contributions to this special issue refer to multiscale aspects related to genetic mutations. The book by Weinberg[29] offers an essential guideline to applied mathematicians for understanding the great complexity of cancer, from the onset of the neoplastic state to progression through successive stages characterized by increasing degrees of malignancy. The main guidelines are reported in the already cited paper.[17]

Therefore, the interactions between the biological and mathematical sciences appears very deep and links high level research activity in biology to sophisticated mathematical methods. The mathematical approach needs to be permanently updated to respond to the challenges coming from biology; hopefully mathematics can contribute to the evolution of biology that is foreseen by the scientific community in this century.[31]

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References

1. T. Alarcon, H. M. Byrne and P. K. Maini, A cellular automaton model for tumour growth in inhomogenous environment, *J. Theor. Biol.*, **225** (2003) 257–274.
2. N. Bellomo, A. Bellouquid, J. Nieto and J. Soler, Multicellular biological growing systems: Hyperbolic limits towards macroscopic description, *Math. Mod. Meth. Appl. Sci.* **17S** (2007) 1675–1692.
3. 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.

4. N. Bellomo and G. Forni, Looking for new paradigms towards a biological mathematical theory of complex multicellular systems, *Math. Mod. Meth. Appl. Sci.* **16** (2006) 1001–1029.
5. 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) 1735–1778.
6. A. Bru and M. A. Herrero, On the physical law of tumor growth, *Math. Mod. Meth. Appl. Sci.* **16** (2006) 1199–1218.
7. N. Bellomo and P. K. Maini, Preface, *Math. Mod. Meth. Appl. Sci.* **15** (2005) iii–viii.
8. N. Bellomo and P. K. Maini, Preface, *Math. Mod. Meth. Appl. Sci.* **16** (2006) iii–vii.
9. H. M. Byrne, M. R. Owen, T. A. Alarcon, J. Murphy and P. K. Maini, Modelling the response of vascular tumours to chemotherapy: A multiscale approach, *Math. Mod. Meth. Appl. Sci.* **16** (2006) 1219–1241.
10. A. Bru, J. M. Pastor, I. Fernaud, I. Bru, S. Melle and C. Berenguer, Super-rough dynamics on tumor growth, *Phys. Rev. Lett.* **81** (1998) 4008–4011.
11. F. Chalub, Y. Dolak-Struss, P. Markowich, D. Oeltz, C. Schmeiser and A. Soref, Model hierarchies for cell aggregation by chemotaxis, *Math. Mod. Meth. Appl. Sci.* **16** (2006) 1173–1198.
12. M. A. J. Chaplain and G. Lolas, Spatio–temporal heterogeneity arising in a mathematical model of cancer invasion of tissue, *Math. Mod. Meth. Appl. Sci.* **15** (2005) 1685–1734.
13. A. Friedman and G. Lolas, Analysis of a mathematical model of lymphangiogenesis, *Math. Mod. Meth. Appl. Sci.* **15** (2005) 95–109.
14. A. Friedman, Mathematical analysis and challenges arising from models of tumor growth, *Math. Mod. Meth. Appl. Sci.* **17S** (2007) 1751–1772.
15. R. A. Gatenby and T. L. Vincent, Evolutionary model of carcinogenesis, *Cancer Res.* **63** (2003) 6212–6220.
16. R. A. Gatenby, T. L. Vincent and R. J. Gillies, Evolutionary dynamics in carcinogenesis, *Math. Mod. Meth. Appl. Sci.* **15** (2005) 1619–1638.
17. D. Hanahan and R. A. Weinberg, The Hallmarks of Cancer, *Cell* **100** (2000) 57–70.
18. N. L. Komarova, A. Sengupta and M. A. Nowak, Mutation-selection networks of cancer initiation: Tumor suppressor genes and chromosomal instability, *J. Theor. Biol.* **223** (2003) 433–450.
19. N. L. Komarova, A. Sengupta and M. A. Nowak, Spatial stochastic models for cancer initiation and progression, *Bull. Math. Biol.* **68** (2006) 1573–1599.
20. N. L. Komarova, Stochastic modelling of loss- and gain-of-function mutations in cancer, *Math. Mod. Meth. Appl. Sci.* **17S** (2007) 1647–1673.
21. Y. Kim, M. A. Stolarska and H. G. Othmer, A hybrid model for tumor spheroid growth *in vitro* I: Theoretical development and early results, *Math. Mod. Meth. Appl. Sci.* **17S** (2007) 1773–1798.
22. 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) 1667–1684.
23. P. L. Lollini, S. Motta and F. Pappalardo, Modelling the immune competition, *Math. Mod. Meth. Appl. Sci.* **16S** (2006) 1091–1124.
24. A. Marchiniak-Czochra and M. Kimmel, Dynamics of growth and signaling along linear and surface structures in very early tumors, *Comp. Math. Meth. Med.* **7** (2007) 189–312.
25. A. Marchiniak-Czochra and M. Kimmel, Modelling of early lung cancer progression: Influence of growth factor production and cooperation between partially transformed cells, *Math. Mod. Meth. Appl. Sci.* **17S** (2007) 1693–1719.

26. M. A. Nowak and K. Sigmund, Evolutionary dynamics of biological games, *Science* **303** (2004) 793–799.
27. R. Reed, Why is mathematical biology so hard?, *Not. Amer. Math. Soc.* **51** (2004) 338–342.
28. B. Vogelstein and K. W. Kinzler, Cancer genes and the pathways they control, *Nature Med.* **10** (2004) 789–799.
29. R. A. Weinberg, *The Biology of Cancer* (Taylor and Francis, 2007).
30. D. J. Wilson, J. R. King and H. M. Byrne, Modelling scaffold occupation by a growing, nutrient-rich tissue, *Math. Mod. Meth. Appl. Sci.* **17S** (2007) 1721–1750.
31. C. R. Woese, A new biology for a new century, *Microbio. Molecular Biol. Rev.* **68** (2004) 173–186.