Problems, Progress and Perspectives in Mathematical and Computational Biology

Qixuan Wang[1,2*†], Hans G. Othmer[3*†] and Philip K. Maini[4*†]

[1]Department of Mathematics, University of California, Riverside, Riverside, California, USA.
[2]Interdisciplinary Center for Quantitative Modeling in Biology, University of California, Riverside, Riverside, California, USA.
[3]School of Mathematics, University of Minnesota, Twin Cities, Minneapolis, Minnesota, USA.
[4]Wolfson Centre for Mathematical Biology, Mathematical Institute, University of Oxford, Oxford, State, United Kingdom.

*Corresponding author(s). E-mail(s): qixuanw@ucr.edu; othmer@umn.edu; Philip.Maini@maths.ox.ac.uk;
†These authors contributed equally to this work.

Abstract

For this Special Collection we invited experts in the area of mathematical and computational biology to share their views on the major problems in their areas of interest and their recent research results – focusing on the development of state-of-the-art modeling approaches and computational techniques applied to problems in the life sciences – and to present their vision of the new directions needed for addressing unsolved problems. Papers in this Special Collection address mathematical and computational problems in several areas of the life sciences, including theoretical neuroscience, cancer modeling, and cell and developmental systems. With respect to methodologies, these papers cover dynamical systems, differential equations, stochastic processes, and modern computational techniques, all with an emphasis on techniques in modern modeling and computational methodologies. This Special Collection is jointly hosted by the Bulletin of Mathematical Biology and the Journal of Mathematical Biology.

Keywords: Mathematical biology, computational biology

1 Introduction

During the past several decades, the scientific community has witnessed rapid development and advances both in experimental techniques in biology, and in mathematical modeling and computational techniques. Development of experimental techniques opens a new world in the life sciences that researchers have not previously been able to access. New modeling concepts and methodologies are emerging to meet the increasing need from modern biology. For this Special Collection "Problems, Progress and Perspectives in Mathematical and Computational Biology", we invited seventeen contributions. They cover a broad range of topics in modern modeling research with applications in the life sciences, using various state-of-the-art modeling and computational methodologies to tackle problems across a range of systems: neuroscience, cell and development systems, and human diseases.

Mathematical oncology, or cancer modeling, remains one of the largest modeling research areas. Nowadays cancer modeling research spans the whole range from mechanistic modeling to data-driven statistical and machine learning approaches, aiming to explore cancer development mechanisms and cancer treatment dynamics, as well as predict cancer development in the future based on knowledge of present and past data. One major question in general mechanistic modeling – including cancer growth modeling– concerns the interaction and integration of biochemical and biomechanical cues. To address this, a thermodynamically-consistent continuum model of growth-elasticity is used to investigate the chemo-mechanical regulation of tumor growth in [15]. In addition to exploring cancer growth mechanisms, mechanistic models are also used to optimize cancer treatment. In recent years, virotherapy has become an emerging and promising cancer therapy. In [13], a combination of numerical analysis and bifurcation analysis is used to study the spatio-temporal virus infection pattern formation dynamics, leading to the minimal speed of travelling invasion waves for the cancer and the oncolytic virus. In [2], the importance of spatial-patterning mechanisms in cancer development, as well as in treatment design and dosing optimization, is highlighted for the case of cancer immunotherapy. In [12], a novel approach is proposed to estimate the patient-specific tumor carrying capacity, based on the logistic growth model.

Neurodegenerative diseases, including Alzheimer's disease, have a serious impact on many people. Therefore, theoretical neuroscience modeling has become an emerging and rapidly developing field. In [8] it is suggested that brain-scale network aggregation dynamics of prion-like neurodegenerative protein may contribute to drug design aimed at preventing whole-brain Alzheimer's disease progression. In the theoretical study of neuronal dynamics, modeling frameworks on both the micro- and network-scale are developed to explore the effects of heterogeneity in synaptic ensheathment on synaptic communication and network dynamics [7].

Apart from disease modeling, cell and developmental biology remains a leading research area in theoretical biology. It ranges from cell fate dynamics, to tissue growth, and includes the general study of reaction-diffusion dynamics. Cell fate determination has been a major research focus in mathematical biology during the past few decades, deeply rooted in Waddington's epigenetic landscape theory. A random dynamical system framework is presented in [14], together with a tutorial outlining the current perspectives on cell fate. In development, domain establishment remains a classic open problem. In [9], a comparison between pattern formation based on diffusion-driven transport vs. cytoneme-regulated transport is made, and the effect of their joint expression is investigated. Analytical results are derived for simple systems, while numerical results are provided for more complex systems. Another type of problem arises in cell biology, where many processes can be modeled using a reaction-diffusion system in a bounded domain (the cell membrane, cytoplasm, etc.), containing a set of small subdomains or interior compartments (such as membrane protein clusters, biological condensates, etc.). Such modeling problems are commonly refered to as singularly-perturbed diffusion problems. [11] presents a review of matched asymptotic analysis and Green's function methods to solve a general type of singular boundary value problem in 2D and 3D, where an inhomogeneous Robin condition is imposed on interior domain boundaries. In another theoretical study, [4] investigates the existence and construction of multiple limit cycles in planar chemical reaction systems, with both algebraic and non-algebraic limit cycles considered.

On the methodology side, we received contributions based on various computational methods, including Boolean networks, agent-based modeling, stochastic modeling, and structured partial differential equation modeling. In addition, some authors have used state-of-the-art topological data analysis as a modeling technique. In each case these papers may serve as tutorials for the community, and provide insights on further development and extension of the methods.

In systems biology, Boolean networks have been widely used for modeling dynamical problems, including cell fate decisions and biological phenotypes. A recent question that arose in Boolean networks studies is the role of motif-avoidant attractors (MAAs). In [3] the authors present a review of the current state of knowledge on MAAs together with novel insights on their regulatory roles. In addition, a large-scale computation of published Boolean models of biological systems verifies the rarity of MAAs in biological systems.

Agent-based models (ABMs) have been widely used for modeling complex biological and biomedical systems, due to their effectiveness in showing how individual behaviors at the microscale level give rise to emergent behaviors at the macroscale level. However, the high computational costs remain a barrier for parameter exploration, sensitivity analysis and uncertainty quantification. In recent years, ABM-based surrogate models have become a powerful tool to assist in analyzing the original ABM. A review of the most widely-used ABM surrogate modeling approaches, including statistical, mechanistic, and machine-learning-based approaches, as well as emerging hybrid approaches, is presented in [17].

Stochastic simulation has been a popular approach to explore various stochastic dynamics, including reaction-diffusion processes. One major question is how to choose the size of the compartments used in stochastic reaction-diffusion modeling. A multi-grid reaction-diffusion master equation (mgRDME) is analyzed in [10], where the grid sizes are allowed to vary across species, but remain constant for each species. Numerical simulations show that mgRDME models allow for high accuracy at reduced numerical cost.

In population dynamics, heterogeneity across individuals may result in dynamical behaviors that do not exist in an ideally-homogeneous population. In recent years, the contribution of phenotypic diversity to population dynamics has been acknowledged. [5] serves as a review of, as well as a tutorial on, phenotype-structured partial differential equation (PS-PDE) models, presenting standard tools and methods that can be used to derive, analyze, and numerically-compute solutions of PS-PDE models. In a theoretical study of phenotype-structured populations, focused on discretely-structured logistic growth models, necessary and sufficient conditions for exact moment closures are derived [6].

Topological data analysis (TDA) is an emerging field of computational mathematics that has been widely applied to biomedical research. While TDA has been widely used in data science over the past few years, this Special Collection contains two contributions that apply TDA to mechanistic modeling, shedding light on a promising future direction that integrates data science and mathematical modeling. In [1], TDA is used to predict the occurrence of tumor niche formation surrounding blood vessels, by analyzing spatio-temporal data of cell locations generated from modeling synthetic data. [16] illustrates an application of TDA to the study of pattern formation, using a topological clustering algorithm to reveal the dependence of pattern topology on parameters.

In summary, this Special Collection provides an overview of various modeling and computational methodologies, as well as example modeling systems. As is stated in the title, the contributions address the prevalent *Problems* in the various areas, present the most recent *Progress* toward addressing these problems, and incorporate useful *Perspectives* that hopefully provide a roadmap for future development in this field.

Supplementary information. Not applicable

Acknowledgements. Not applicable

Author contributions. Q Wang, H. G. Othmer and P. K. Maini contributed to the study, conception, design, manuscript writing and revision.

Declarations

Conflict of interest. The authors have no conflict of interest to declare that are relevant to the content of this article.

References

[1] Yang, J., Fang, H., Dhesi, J., Yoon, I.H., Bull, J.A., Byrne, H.M., Harrington, H.A., Grindstaff, G.: Topological classification of tumour-immune interactions and dynamics. Journal of Mathematical Biology **91**(3), 25 (2025)

[2] Brennan, M., Krause, A.L., Villar-Sepúlveda, E., Prior, C.B.: Pattern formation as a resilience mechanism in cancer immunotherapy. Bulletin of Mathematical Biology **87**(8), 1–31 (2025)

[3] Pastva, S., Park, K.H., Huvar, O., Rozum, J.C., Albert, R.: An open problem: Why are motif-avoidant attractors so rare in asynchronous Boolean networks? Journal of Mathematical Biology **91**(1), 11 (2025)

[4] Craciun, G., Erban, R.: Planar chemical reaction systems with algebraic and non-algebraic limit cycles. Journal of Mathematical Biology **90**(6), 64 (2025)

[5] Lorenzi, T., Painter, K.J., Villa, C.: Phenotype structuring in collective cell migration: a tutorial of mathematical models and methods. Journal of Mathematical Biology **90**(6), 61 (2025)

[6] Walker, B.J., Byrne, H.M.: On discretely structured growth models and their moments. Bulletin of Mathematical Biology **87**(6), 71 (2025)

[7] Garcia, N., Reitz, S., Handy, G.: Extending mathematical frameworks to investigate neuronal dynamics in the presence of microglial ensheathment. Bulletin of Mathematical Biology **87**(5), 1–32 (2025)

[8] Brennan, G.S., Goriely, A.: A network aggregation model for amyloid-β dynamics and treatment of alzheimer's diseases at the brain scale. Journal of Mathematical Biology **90**(2), 22 (2025)

[9] Stotsky, J., Othmer, H.G.: The role of cytonemes and diffusive transport in the establishment of morphogen gradients. Bulletin of Mathematical Biology **87**(2), 21 (2025)

[10] Erban, R., Winkelmann, S.: Multi-grid reaction-diffusion master equation: applications to morphogen gradient modelling. Bulletin of Mathematical Biology **87**(1), 6 (2025)

[11] Bressloff, P.C.: Cellular diffusion processes in singularly perturbed domains. Journal of Mathematical Biology **89**(6), 58 (2024)

[12] Pasetto, S., Harshe, I., Brady-Nicholls, R., Gatenby, R.A., Enderling, H.: Harnessing flex point symmetry to estimate logistic tumor population growth. Bulletin of Mathematical Biology **86**(11), 135 (2024)

[13] Baabdulla, A.A., Hillen, T.: Oscillations in a spatial oncolytic virus model.

Bulletin of Mathematical Biology **86**(8), 93 (2024)

[14] Vittadello, S.T., Diaz, L., Liu, Y., Zanca, A., Stumpf, M.P.: Towards a mathematical framework for modelling cell fate dynamics. Journal of Mathematical Biology **91**(5), 1–43 (2025)

[15] Olaranont, N., Wei, C., Lowengrub, J., Wu, M.: Chemomechanical regulation of growing tissues from a thermodynamically-consistent framework and its application to tumor spheroid growth. Journal of mathematical biology **91**(3), 31 (2025)

[16] Spector, R., Harrington, H.A., Gaffney, E.A.: Persistent homology classifies parameter dependence of patterns in Turing systems. Bulletin of Mathematical Biology **88**(1), 10 (2026)

[17] Norton, K.-A., Bergman, D., Jain, H.V., Jackson, T.: Advances in surrogate modeling for biological agent-based simulations: Trends, challenges, and future prospects. Journal of Mathematical Biology **92**(1), 6 (2026)