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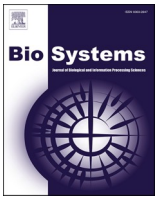

Editorial: Computational approaches in cancer modelling

1. Introduction

Our understanding of cancer complexity has been dramatically improved in the last 20 years. Perou et al. (2000) started the revolution by demonstrating that the breast cancer is not a single disease but comprised of numerous subtypes based on their gene expression patterns. With the advance in gene profiling, the striking diversity of other cancer types has been discovered. The development of new animal models and more precise cell-based analytical techniques helped to establish the role of cancer stem cells (Wicha et al., 2006) and the tumour microenvironment (Balkwill et al., 2012; Jin and Jin, 2020) in tumorigenesis and metastasis. Now we are at the crossroad. Any new aspect of tumour organization, heterogeneity and diversity we unravel can lead to a new therapeutic target. These advances created the possibility of wider application of personalized medicine by matching the right approach with the right patient at the right time. However, the multitude of different treatments (immunotherapy, chemotherapy, radiation, surgery) created a problem of how to combine and optimize the treatments to help patients. To blindly test all combinations of the treatments is unfeasible (for ethical and practical reasons). Therefore, the second stream of research focused on the systems biology of cancer and the development of new conceptual models is needed more than ever.

Only such broad view will make it possible to model cancer as a self-organizing, adaptable phenomenon that interacts with an organism in numerous ways (Coffey, 1998; Deisboeck and Couzin, 2009; Jamous et al., 2020). For example, cancer stem cells can differentiate into multiple types of cancer cells, while some of them can dedifferentiate back to embryonic-like stemness. The level of dedifferentiation depends on the cell type, the type of stressors, and the duration of stress. Such emergent collective behaviour stems from a network of cell-cell interactions and numerous (direct or indirect) feedbacks within the tumour microenvironment. As a result, tumours can fight back by developing drug resistance and initiating metastasis (Marusyk et al., 2020). However, we are far from understanding the processes that lead to such emergence. To model and validate them with experimental data, we need to develop a new set of conceptual, modelling and experimental tools (or to adopt them from other disciplines). For example, with tools from complex network analysis, we can use single-cell level interactions to analyze large-scale network interaction patterns (both spatial and temporal). By applying the ensemble modelling approach (a common practice in climate science) we can develop an integrated and systematic analysis of a wide range of model assumptions. Finally, with machine learning, we can speed-up the harmonization of experimental data, their metadata enrichment, and comparison of different models and their dynamics.

With the application of nanomedicine, the problem became even more complex. By associating drugs with different nanocarriers we can modify their efficacy and biodistribution (for a review, see for example Tran et al., 2017). A recent review by Stillman et al. (2020) summarises efforts to build multi-scale models to automatically design cancer nanomedicine. A preliminary framework was designed to grow virtual tumours, including cancer stem cells, and automatically discover treatment strategies based on modifying nanoparticle designs using artificial evolution (Stillman et al., 2021). This opens the door to using modelling to both capture the self-organised nature of tumour development, and the complexity of large numbers of nanoparticles interacting within a patient, their tumours, and with each other, leading to the prospect of cooperative nanosystems (Hauert and Bhatia, 2014).

Due to the high complexity of the problem, mathematical modelling, model analysis and computer simulations, all under the umbrella term of mathematical oncology, are indispensable. Recently, mathematical oncology came of age and has begun to migrate from mathematics toward being a subdiscipline of oncology itself (Rockne and Scott, 2019). Such direction is commendable, but much needs to be done to reach the stage where mathematical modelling, experimental research and clinical trials will closely interact and guide each other. Therefore, for this Special Issue, we have invited scholars to investigate novel computational and modelling approaches that will cover multiple spatial and temporal scales of cancer models, but also possible frameworks that will integrate them. The issue contains 15 papers covering different aspects of the mathematical oncology that can be clustered in 4 main thematic areas: search for more personalized therapies, molecular-scale modelling, applying novel mathematical tools and developing models of cancer initiation and growth.

2. Short presentation of each paper

The largest portion of this Special issue is devoted to optimizing treatment of different cancer types. For breast cancer, Nave et al. (2020) developed a mathematical model, called a singular perturbed system, based on the use of non-linear ODEs with a hidden hierarchy. Using this model they developed an optimal vaccination protocol of different doses depending on tumour size. For the same tumour type, Guo et al. (2021) used weighted gene co-expression network analysis to identify functionally related gene networks and divide breast cancer into different prognostic modules. They showed how it can be used for identifying prognostic modules for breast cancer. For AIDS-associated Kaposi's sarcoma, Kaondera-Shava et al. (2021) modelled the effect of viral load on Kaposi's sarcoma tumour progression and showed that appropriate

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antiretroviral treatment strategies can significantly reduce tumour burden. Lazebnik et al. (2021) focused on bladder cancer. They took into account the initial distribution of the cancer cells in the geometry of the bladder and investigated customized treatments based on tumour polyp depth in the urothelium. They further analyzed time-optimal personalized treatment protocols based on initial tumour distribution. Finally, Allali (2021) modelled the link between early-stage cervical cancer and HPV infection. He showed that control of HPV infection can also act on reducing the amount of precancerous and cancerous cells.

On a more general scale, three papers investigated cancer initiation and growth. To investigate bottom-up drivers of cancer development, Akhavan-Safar and Teimourpour (2021) developed KatzDriver, a network-based approach to detect cancer driver genes. It is based on calculating the relative impact of each gene on the spread of abnormality in the gene regulatory network. On the other hand, Lahoz-Beltra and Juárez Rodriguez (2020) take a top-down approach. They investigated how, in a virtual patient, depression, stress or similar altered state of mind can lead to disturbed hormone levels that will eventually lead to a condition of chronic inflammation. They hybridized a chatbot for the simulation of the state of mind with differential equations simulating both the hormones of the hypothalamic-pituitary-adrenal axis and the cytokines involved in the mechanism of cellular inflammation. On an even more general scale, Sauer et al. (2021) developed a theoretical framework to predict the increase in the size of the cell cluster as a function of its structure, and also to predict the critical cluster sizes that mark the transitions from one distinct cluster configuration to the next.

Down to the molecular level, we have two papers. Bhattacharya et al. (2021) investigated conformational changes in the Integrin αV subunit that is involved in regulating angiogenesis and thus cancer progression. Kovacevic et al. (2021) used atomistic molecular simulations to study how the size, hydrophobicity, and concentration of the anti-cancer drug affect the structure of functionalized gold nanoparticles. Their simulations demonstrated how the physico-chemical properties of drugs and ligands used in developing novel nanosystems can significantly alter the properties of nanoparticles and their potential efficacy.

Vast layers of cancer complexity, nicely reflected in a wide scope of papers described above, point to the need of using novel mathematical tools and/or novel approaches in machine learning, to more efficiently explore tumour models and clinical treatment. Valentim et al. (2021a, 2021b) explored possibilities of using fractional calculus in mathematical oncology. They demonstrated the superiority of this approach in describing the experimental data, thus offering an interesting new perspective for modelling tumour growth. Nave et al. (2021) combined a mathematical model of chemotherapy treatment for breast cancer with clinical datasets and with linear regression and neural network algorithms to predict tumour size at different time points. They showed that merging clinical data with the model greatly improves the machine learning predictions. Wu et al. (2021) used random forest and greedy algorithm to define sets of competing gene pairs that can help in distinguishing clear cell renal cell carcinoma subtypes. Finally, Balaz et al. (2021) developed a machine learning open-ended model to explore the design space of adaptable therapies. Combining evolvable therapeutic agents with an adaptable tumour where different phenotypes of cancer cells emerge, they demonstrated the emergence of continuously optimizing therapies.

3. Conclusions

Building on the work presented here, and other similar efforts (e.g. Anderson and Maini, 2018; Rockne and Scott, 2019), there is a potential to integrate across models and scales to look at the cancer system as a whole. However, without a clear roadmap, the field of mathematical oncology will remain largely fragmented and uncoordinated. Several issues should be addressed, discussed and agreed upon within the community. First, what is the goal of a specific model? To mechanistically understand tumour initiation, evolution, progression and physiology, or to descriptively represent tumour population dynamics, or to model specific treatment effect? The precise definition of the modelling goal will lead to the application of different strategies in all the following questions. Second, how to standardize the collection of experimental data and their translation into model parameters? Third, what level of uncertainty (in both parameter estimation and reporting of obtained simulation results) is tolerable? Fourth, how to ensure exchange, reuse and integration of different models into a multiscale pipeline? Fifth, what should the performance metrics be for different modelling goals and what is the minimum set of data analysis needed to claim whether the performance is achieved?

Some preliminary steps towards such comprehensive roadmap are already made. *The 2019 mathematical oncology roadmap* by Rockne et al. (2019) is a great collection of diverse research programs. However, to reach the ultimate goal of integrating mathematical modelling into pre-clinical and clinical practice, even more is needed. A common platform and a tight collaboration between mathematical oncologists and researchers in diverse biological and clinical fields are necessary. Only in such collaboration researchers from different fields will mutually guide each other in designing experimental research, collecting and reporting data and adapting mathematical models following experimental constraints. We believe that the first step in making such widespread collaboration possible is by reaching a consensus on all the issues raised above. Further coordination can be conducted by an international body similar to IPCC (Intergovernmental Panel on Climate Change); an authoritative body that studies and validates a set of well-established models and coordinates their improvements.

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