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Comment

Combining dynamic modeling with machine learning can be the key for the integration of mathematical and clinical oncology Comment on "Improving cancer treatments via dynamical biophysical models" by M. Kuznetsov, J. Clairambault, V. Volpert

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The authors in [1] had made an amazing job in reviewing the vast literature of tumor dynamical modeling. Recently the amount of mathematically oncology papers has been significantly increased over the last 30 years [2]. Moreover, the topics covered in mathematical oncology studies vary from identification and analysis of biophysical mechanisms to proposing and optimizing new therapies. The authors managed to strike a balance in this vast ocean of papers and highlighted the main achievements in the field. Here, I would like to focus on the main question posed by the authors in the Discussion of the paper: why mathematical models are not so successful in the clinics and how can we improve this.

The vision of mathematical modeling in Oncology is to provide personalized predictions by taking into account patient-specific data. In clinical practice, cancer patients undergo a plethora of examinations that span from high-throughput -omic techniques, blood sample analysis, clinical imaging (e.g. CT, MRI) or biopsy sampling, to name a few. However, such clinical data are provided for very limited time-points since data collection is restricted to patient's clinical presentation. Moreover, the mechanistic connection between these data is elusive due to their multiscale nature. For instance imaging data, such as MRI, typically provides an organ level picture of a disease (macroscopic), biopsies represent cellular patterns at a tissue (mesoscopic) level and -omics or FACS allow for sub-cellular insights (microscopic). Currently, we have limited biological knowledge to connect all these variables in a single model, as already suggested by the authors. Therefore, many of these data variables will be left out from the model development process.

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Now, even if we had the all the required mechanistic knowledge to write appropriate equations, such a model would involve a huge number of parameters. In combination with the lack of clinical data with sufficient temporal resolution and specificity, the goal of personalized model calibration would have been a mission impossible. Under this constraint, delivering personalized predictions becomes a daunting task. In a nutshell, the current challenges of personalized mathematical oncology are: (C1) circumvent the problem of biological complexity and the missing mechanistic knowledge, (C2) exploit the predictive power hidden in non-modellable data.

To treat the afore-mentioned challenges the combination of biophysical dynamic models and machine learning methods bears a realistic promise. It has been already recognized that the combination of data intensive methods and multiscale modeling could revolutionize the field [3,7]. Physics-informed machine learning methods have been recently proposed in the context of engineering applications [4]. For instance, physics-informed neural networks (PINNs) can integrate the knowledge of any physical laws that dictate a given dataset and can be described by partial differential equations [5]. In this way, they overcome the low data availability of some biological and engineering systems. Recently, it has been developed a Bayesian combination of machine learning and mechanistic modeling (BaM^3) [6] that allows for improved clinically relevant predictions. The method uses mechanistic model predictions as intelligent priors, even when mechanisms and parameters are partially known (C1). In turn, it corrects model predictions by harnessing the predictive power of infrequent non-modellable data (C1, C2). The BAM^3 framework has been successfully tested on two real cohorts of patients with leukemia and ovarian cancer. Similar endeavors can revolutionize the future of mathematical oncology. In general, I believe that integrating mechanistic modeling with machine learning methods can open the door for the penetration of mathematical oncology in the clinics.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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