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OPEN LETTER

Towards personalized medicine by mathematical modeling of tumors

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Abstract

In this open letter, we give some insights on the potential use of mathematical modeling in understanding cancer research. The article is written in a form that can be understood by a larger public, not only by specialists.

Keywords

mathematical modeling; cancer models

This article is included in the Horizon 2020 gateway.

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Open Peer Review

Approval Status ✓ ✓

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2. **Adriana Buică**, Babeș-Bolyai University, Cluj-Napoca, Romania

Any reports and responses or comments on the article can be found at the end of the article.

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On applications of mathematical modeling

In the modern world, cancer is one of the leading causes of death, with almost 2 million new cases and 600,000 deaths in the USA alone in 2020[1]. Still, intensive research is carried out to treat tumor cells, starting from the classical chemotherapy, towards more specific therapies, like targeted molecular therapies and immunotherapies. Many oncologists believe that classical chemotherapies have reached their maximum efficiency and cannot be further enhanced. Although, other researchers do not agree with this.

The current chemotherapy protocols are based on the maximal tolerable dose (MTD), which is injected with a predefined schedule, attacking the tumor and the body of the patient aggressively like "carpet bombing". A promising new direction of therapy development is optimization of the protocol, that is, use as large dose as necessary, at the time it is necessary. However, it is very hard to identify the necessary dose and time of injection. This is where an approach based on mathematical modeling comes into the picture[2].

The application of mathematical models in clinical practice relies on strong collaboration with medical experts who have limited knowledge on mathematical modeling and, particularly, the theory of differential equations. The cooperation can be boosted if we describe the mathematical laws (such as equations and constraint conditions) in the way they can be interpreted by biologists as well. Our research group at the Physiological Controls Research Center of Obuda University uses formal reaction kinetics analogy[3] and[4] to interpret tumor modeling for experts not familiar with differential equations.

Although a mathematical model is fundamental for the optimization of drug therapies, it is only a first step towards personalized medicine. There are many issues that need to be solved. The first one is the identification of the model parameters, which gives rise to several problems such as:

1. Since in experiments we can only measure the total tumor volume and have limited number of measurements, the parameter set describing the behavior is not unique; there are infinitely many parameter sets such that the model gives the same output.

2. The parameters change over time, since the tumor adapts to the treatment, and the patient is also affected by the chemotherapy.

3. The system is impulsive, that is, the inputs are injections, and they introduce discontinuities in the model.

On the other hand, these problems give rise to interesting new approaches, like application of artificial intelligence and nonlinear optimization algorithms for the physiological problem. Finding the optimal set of injections is also challenging, due to the limited measurements on the system and the inaccuracies in the parametric identification, and also by the impulsive nature of the system. Application of nonlinear optimization techniques shows a potential way towards personalized treatment, however, increasing robustness is still subject to further research.

Mathematical modeling in biology and, particularly, in cancer research has the potential of reducing considerably the costs of the research, which usually arise from various laboratory-based experiments. Once the biological laws of the disease's evolution are known up to a good extent, they often can be described by theoretical mathematical models, based on a variety of methods and tools. The analysis of these models contributes, in turn, to a better understanding of the disease, thus, new opportunities for finding solutions to these abnormalities may arise.

In conclusion, the optimization based on mathematical modeling is a promising direction towards personalized medicine. The first step is creating relevant mathematical models of the problem, which need to be validated by experiments. However, after this first step, there is still a long way to go until personalized medicine can be used in clinical practice.

2 Data availability

No data are associated with this article.

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✔ **Adriana Buică**
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This article supports the use of mathematical modeling of tumors with the aim of introducing a personalized treatment of cancer. This is a noble and ambitious target and, as the authors also emphasized, difficult to realize. Based on their experience, they proposed the use of differential equations, artificial intelligence, and nonlinear optimization algorithms. They also discuss issues on the challenges of the cooperation between the medical experts and the mathematicians.

Is the rationale for the Open Letter provided in sufficient detail? (Please consider whether existing challenges in the field are outlined clearly and whether the purpose of the letter is explained)
Yes

Does the article adequately reference differing views and opinions?
Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language? (Please consider whether all subject-specific terms, concepts and abbreviations are explained)
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow? (Please consider whether others in the research community would be able to implement guidelines or recommendations and/or constructively engage in the debate)
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: mathematics (differential equations)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 20 May 2022

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Andrea De Gaetano
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This is a letter directed to the general public, and its language is appropriate for the scope.

My only doubt refers to the introduction of artificial intelligence or similar techniques as an alternative modelling approach right after having stated (correctly) that data insufficiency often prevents (structural) model identification. It is not clear how artificial intelligence would improve the situation.

Is the rationale for the Open Letter provided in sufficient detail? (Please consider whether existing challenges in the field are outlined clearly and whether the purpose of the letter is explained)
Yes

Does the article adequately reference differing views and opinions?
Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language? (Please consider whether all subject-specific terms, concepts and abbreviations are explained)
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow? (Please consider whether others in the research community would be able to implement guidelines or recommendations and/or constructively engage in the debate)
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: mathematical modelling in biomedicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.