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Reply to comment

Perspectives in cancer treatment
Reply to comments on "Improving cancer treatments via dynamical biophysical models"

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We would like to thank the authors of the comments [1–5] for their interesting and stimulating ideas, as well as for discussing some issues that remained outside the scope of our review [6]. We agree with these comments and we will return to some of them in the discussion below.

1. Different modeling approaches

1.1. Model simplification

We share the opinion of Tommaso Lorenzi in his comment [5] about different modeling approaches. We advocate that the models to be used in improving cancer therapeutics, are minimal ODE- or PDE-based models, which seem to us preferable if one wants to propose optimization and optimal control methods. This comment has also been rightly underlined that continuous models based on structured PDEs are more soundly established when they have been derived from agent-based models (ABMs), which we mentioned, writing that passage to the limit in number and size

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of cells is hard to justify, and that they should rely on mean-field representations of cellular dynamics, which we did not mention as such.

As it is stressed in the comment by Jack A. Tuszynski [1], modeling research is more often computational than analytical. Even though theorems in mathematical oncology are rare (but not absent), they are just the same the grail, and computational models - experimental mathematics, in some sense - are often what we must humbly content ourselves with, offering mathematical conjectures that may guide us towards proving theorems, and this is sometimes the case in studying asymptotic behavior of the systems at stake.

1.2. Model extension

The discussion of reduced and more complete models is continued in the comments by Heiko Enderling [2], Angélique Stéphanou [3] and Haralampos Hatzikirou [4]. Indeed, we chose minimal models for the above mentioned reasons, rather than models based on systems biology meant as relying on extended systems of equations representing intracellular gene regulatory networks (GRNs) and the main connections between them, represented by known excitatory or inhibitory molecular influences between the main genes at stake. This is another way of approaching the reality of intracellular dynamics, which we did not choose, as it needs a tremendous harvest of data to identify the numerous parameters of such models, which may possibly be helped by artificial intelligence (AI) and deep machine learning (ML), as advocated by so many biologists today. One of the comments suggests an integrated combination of Bayesian techniques applied to mechanistic models with ML in multiscale models [4]. Such descriptive methods, that require masses of data - that for sure biologists are eager to provide because most often they have them in stock and do not know how to deal with them - can indeed aid, e.g., in estimating parameter values and identifying crucial factors that need to be accounted for in reduced dynamical models. However, we contend that, a biological phenomenon being given with possible disruptive dynamics, such as tissue differentiation and proliferation perturbed in cancer, one should focus on a limited set of pathophysiological tracks that are likely to be at work in disease and amenable to theoretical therapeutic correction by action on precise terms in equations, representing physiological targets. Only by having such simple phenomenological systems at hand, that represent a given therapeutic action on a given disrupted biological system such as a cancerous cell population, can one propose improving, if not optimizing, therapeutic control.

It is not surprising, in this perspective, that comments advocating describing proliferation in health and in disease using big GRN systems [2] may consider our focus on optimization and optimal control in cancer therapeutics as too big a hurdle to provide the success stories that we are all awaiting to be able to convince oncologists of the utility of physically based mathematical models in therapeutics. Of course, such focus makes us introduce simplifications - which we always demand to be based on physiological bases - to represent the evolution of the systems at stake, in health and in disease, that many biologists will not accept, as too simplifying. However, reduction of physical reality by such simplifications is at the base of all physics, and it is on the other hand mandatory to have access to an improved understanding of the dynamics of the system at stake and of its possible correction. This goal, therapeutic optimization, determines our focus on minimal models, that is commended in one of the comments [1].

2. Interdisciplinarity and cancer theories

An important feature of our paper, stressed by one of the comments [3] as its main added value, is the importance of making precise, as much as possible, the underlying theories ("philosophy of cancer") that are most often only implicit in the works of cancer biologists. Here we have indeed mentioned SMT, TOFT and the atavistic theory of cancer as scientific attitudes that determine choices of biological observations and experimentations in oncology, be the observers/experimenters conscious of it or not. We agree with this point of view emphasized by the comments.

Discussion of the interaction between modelers and clinicians was continued in the comment [2]. One can contend that it is not true that the lack of a common language limits the direct interactions between mathematicians - and physicists alike - and physicians, as double training programs are more and more proposed in various universities and institutions worldwide. Nevertheless, the reader should be attentive to the last paragraph of Section 5.1. A common language may exist, however if the oncologist just considers the mathematician as a math provider to solve the problems he has in mind, and if conversely the mathematician considers these problems as just food for thought, then such common language does not lead to shared understanding.

One of the comments stress the fact that modelers may often fail to adequately communicate model assumptions and model uncertainties [2]. True. But do oncologists actually ask about such model limitations? In the collaborative experience of at least one of us, the goal of collaboration with mathematicians was presented as "allowing us [clinicians] to think cancer therapeutics differently". A minimal step for sure, however not sufficient to take a maximal advantage of such interdisciplinary collaboration. To this goal, oncologists actually trained in maths at a high level, and mathematicians actually trained in clinical oncology are needed for both to be able to share a common spirit, and not only language, in conceiving new therapeutic tracks. And here the so-called "philosophy of cancer" can help both towards acquiring such spirit. By the word "spirit", that may seem ostentatious to many, we mean not some spiritual common conception of life, but just a constant, insatiable, need to understand the ways of thinking of the other in such collaborative couples. A hard task indeed.

3. Methods of cancer treatment

3.1. Tumor treatment fields by alternating current

One of the important questions, which remained beyond the scope of our review [6], was brought to the discussion by J.A. Tuszynski in his comment [1]. It concerns tumor treatment by alternating electric current with specifically chosen frequency and voltage. The method of tumor treating fields (TTfields) was suggested by Kirson et al. in 2004 [7] and then further developed in later works [8,9]. It was shown that alternating current with intermediate frequencies 100-300 kHz can delay or stop completely cell proliferation and lead to cell death. This effect is based on a subtle interaction between electric field and electrically charged biological molecules and organelles inside the cell. Remarkably, it acts on microtubule formation preventing normal functioning of mitotic spindle. The biophysical background of this complex phenomenon is minutely described in the review [10]. Besides, alternating current can destroy dividing cells before complete cell separation. Due to the interaction of nonuniform electric field near cleavage furrow and alternating current, dipole particles inside the cell move to the separation point and damage cell membrane. Animal studies and clinical trials show that TTfields slow down tumor growth and formation of metastases [9,11]. It is also important that the frequencies of TTfields depend on cell lines and can differ for normal and tumor cells, therefore, decreasing side effect of proliferating cell death. Combination of chemotherapy and TTfields is a promising avenue in cancer treatment.

We also agree with the comment in [1] that mathematical modeling and numerical simulations can be useful in the understanding of these biophysical phenomena and their quantitative assessments. The effect of alternating current on cell membrane and subcellular structures, including microtubules [10], provides an interesting example of complex phenomena where theoretical modeling can lead to important practical results related to cancer treatment.

3.2. Radiotherapy

Heiko Enderling in his comment [2] indicated two ongoing clinical trials founded on the results of mathematical optimization tasks. Another example of ongoing integration of theoretical results into practice is related to the work by Leder et al. [12], also mentioned in his comment – a protocol based on the one suggested in that work has recently been tested for safety in a clinical trial.

Therefore, the influence of mathematical optimization in radiotherapy becomes quite notable. The integration of mathematical modeling in radiobiology is dictated not only by a long history of using mathematics to quantify tumor control and adverse effect probabilities, as rightly pointed out by Heiko Enderling. Another factor is the potential outcome of such collaboration. Radiotherapy is administered to approximately half of the patients diagnosed with cancer, and given its wide use it was suggested by radiobiologists that optimization of radiotherapy should even be a more efficient way than exploiting newly developed drugs to achieve a comparable notable increase in the overall cure rate of cancer [13].

The now being tested in clinics concept of temporally feathered radiation therapy deals with a type of optimization that we have not accentuated in our review, namely, the spatial optimization of irradiation. Along with temporal fractionation, it is an option to increase the treatment efficacy and/or to reduce side-effects associated with the damage to the normal tissues. Spatiotemporal optimization of irradiation is therefore a significant problem, which solution can benefit from mathematical modeling. It is especially relevant, e.g., for intensity modulated radiotherapy and proton

therapy that allow flexible adjustment of the spatial distribution of irradiation. Generally, in practice the main goal is to reduce the dose of radiation administered to the normal tissue, while the tumor volume is generally uniformly irradiated. However, as was noticed in our review, the growing tumor has non-uniform radiosensitivity of its cells and this fact can be taken advantage of for treatment optimization. Notably, based on this fact, as early as in 2000 it was suggested that a non-uniform dose distribution or so-called dose staining based on information obtained by imaging methods could increase radiotherapy efficacy [14]. However, only a rather small number of related experiments have been performed and yet only a few theoretical works exist that consider such tasks.

Summarizing this discussion, we express our hope that new generations of researchers with interdisciplinary training and profound understanding of cancer theories and practice will contribute to the optimization of cancer treatment and to the development of new methods of treatment. Some possible directions of this important work are discussed above.

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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