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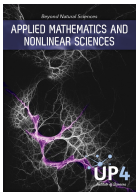

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Applied mathematics and nonlinear sciences in the war on cancer

Víctor M. Pérez-García[1†], Susan Fitzpatrick[2], Luis A. Pérez-Romasanta[3], Milica Pesic[4], Philippe Schucht[5], Estanislao Arana[6], Pilar Sánchez-Gómez[7]

[1]Instituto de Matemática Aplicada a la Ciencia y la Ingeniería and Departamento de Matemáticas, E.T.S.I. Industriales, Avda. Camilo José Cela 3, Universidad de Castilla-La Mancha, Ciudad Real, SPAIN.
[2] James S. Mc. Donnell Foundation, USA.
[3] Radiation Oncology Department, Hospital Universitario de Salamanca, Salamanca, SPAIN.
[4] Department of Neurobiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Despota Stefana 142, Belgrade 11060, SERBIA.
[5] Neurosurgery Department, Bern Inselspital, Bern, Switzerland. SWITZERLAND.
[6] Fundación Instituto Valenciano de Oncología, SPAIN.
[7] Neuro-oncology unit. Health institute Carlos III-UFIEC, SPAIN.

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Abstract

Applied mathematics and nonlinear sciences have an enormous potential for application in cancer. Mathematical models can be used to raise novel hypotheses to test, develop optimized treatment schedules and personalize therapies. However. this potential is yet to be proven in real-world applications to specific cancer types. In this paper we discuss how we think mathematical knowledge may be better used to improve cancer patients' outcome.

Keywords: Mathematical oncology; cancer models; mathematical medicine
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1 Cancer and mathematics: Some facts

Cancer is a major health problem in the industrialized world being the second leading cause of death in the USA and EU after heart disease. A huge quantity of resources is spent every year on cancer research, resulting in

†Corresponding author.
Email address: victor.perezgarcia@uclm.es

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a small, yet sustained, reduction in cancer death rates (in the last ten years this was about $1-2\%$ per year in the US) [1]. However, there is a widespread concern about the slow pace at which these discoveries in fundamental biology are translated into safe and effective clinical interventions.

Statistics is already considered to be a basic ingredient of medical education and routinely used in research, specifically in clinical studies. This is so even when many physicians have a limited understanding of statistics and risk analysis [2]. However, the potential of other mathematical tools such as differential equations, advanced numerical methods, optimization, etc, have not been broadly incorporated into medical research on clinical care. This is so in spite of the fact that these methods are part of the standard toolbox of the applied mathematician that have proven useful in many other fields of science and engineering.

All of biomedical research relies on the use of experimental models all with strengths and limitations. Mathematical models instead describe real systems by means of abstraction and mathematical formalism. They contain equations trying to describe the real system's behavior using the real quantities to be described as mathematical variables within the model. They enable extrapolation beyond the situations originally analyzed, allowing researchers to make quantitative predictions, inference of mechanisms, falsification of underlying biological hypotheses and quantitative description of relationships between different components of a system. Mathematical models are limited because they cannot replace experimental results obtained by other biomedical models such as cell lines, research animals or clinical trials. Their advantage over experimentation is in providing a broader picture that may help novel findings and even solutions for some cancer-related problems. Moreover, they could improve clinical care of patients by increasing the use of tools from applied mathematics and incorporating such approaches into biomedical models of disease (see e.g. the reviews [3–12]).

Mathematical "dynamical" models have already been the basis of many theoretical proposals including: tumor control [13–15], adaptive therapies [16], metronomic [17, 18] or protracted [19] therapies, implementing concepts from evolutionary dynamics [20–22], non-Darwinian dynamics [23], therapy personalization [24–28], to cite a few of very many examples. In addition, the definition of quantitative measures of the disease such as novel imaging biomarkers may benefit from the use of mathematical ideas [27, 29–31].

The first textbooks treating mathematical oncology as a unified subject are appearing [22, 32] suggesting a maturing of the field.

Furthermore, a search in the Web of Science database provides more than 6000 results for "mathematical model" and "cancer" (including statistical models); 537 results for "cancer" and "differential equation" and 912 on "cancer" and "mathematics". Thus, on the basis of such a large number of results, one would expect applied mathematics and nonlinear sciences to have played a substantial role in cancer research. This is not the case, however. Simple mathematical models such as the LQ model [33] are used for radiotherapy planning, and many other mathematical applications are hidden in image reconstruction or in different aspects of radiotherapy, but the direct impact of applied mathematics in oncology has been negligible. No oncologist in the world chooses a specific therapy or fixes the doses or the time course of drug administration on the basis of non-trivial mathematical models. Some mathematicians will probably think this is due to the limited training of physicians in advanced mathematics, but what needs to grow probably are collaborations. We will elaborate on this through this paper.

This paper does not intend to be a review of the accomplishments in the mathematical description of cancer-related phenomena. There are excellent recent reviews and books on that [3–12, 22, 32]. Instead, our goal is more 'philosophical', as we will try to describe why mathematics has had so limited impact in oncology, what can be expected from applied mathematics in the war on cancer and how we can close the gap between mathematics and oncology. Considering this last question, we have intentionally written this paper in a non-technical style (i.e., without mathematical equations) as we hope it may be useful for applied mathematicians, physicians and biologists interested in the field.

2 Some reasons for the limited use of 'applied' mathematics in oncology

2.1 The gap between clinicians and basic scientists, the "holy grail" of translational research

The term *translational research* describes all scientific investigation aimed at transferring basic discoveries into new methods for diagnosing, preventing, and treating tumors. However, it is a two-way process as it also implies taking results from the clinic and creating models to understand the efficacy of health care interventions in order to improve them. However, no matter how good it sounds, a number of obstacles –scientific, institutional, cultural, and policy-related – limit the bidirectional flow of information. This kind of work is best conducted through multi- and interdisciplinary collaborations, which are difficult to establish and maintain in current research environments – encouraging specialization and rewarding individual achievement and hypothesis-driven research. In fact, many basic scientists, including mathematicians, may prefer this kind of investigation rather than the goal-directed or descriptive research often conducted with humans in clinical research settings. On the other hand, clinical scientists may think that their work has greater relevance to human health and disease and disregard basic results. Nevertheless, even when both types of scientists are open to translation, they do not necessarily speak the same language because of differences in training and experience.

Trust is also a big issue as there is a basic misconception that mathematical models are "simulations" in a way model organisms or cells are not.

Many cancer-related institutions, at different levels, are becoming aware of the necessity of creating successful translational research environments that would promote interaction between those who have clinical understanding of this disease and those who have training and expertise in fundamental biology, the molecular mechanisms of cancer, and the use of different models (including mathematical ones) [34].

2.2 Experimental researchers and physicians are not aware of the potential of mathematical modelling

The power of mathematical modeling is mostly unknown to biomedical scientist in general, and to clinicians in particular. The value of mathematics for real-life problem solving is not usually part of their education or, when it is, the examples proposed are academic (and useless). Even those who follow more advanced mathematical modeling courses at university find this to be often unrelated to the issues they have to face on a daily basis.

To most people, including many biologists and physicians, mathematical models are an esoteric, mysterious scientific instrument. In part, this is because of the mystique that shrouds many mathematical techniques, but also because the concept and role of mathematical models are poorly understood. However, there is nothing arcane or mysterious about mathematical models. On careful examination, they turn out to be common sense reduced to calculation [35]. In any case, mathematics is perceived by biomedical scientists, notable exceptions aside, as a method for generating academic problems rather than a way of solving real-life ones. May be this is in part due to the fact that biology emerged historically from observational natural history unlike phsics where mathematics is an integral part of it. In fact, mathematics and physics they both grew together. On the contrary, mathematical biology, having joined biology much later, sits as a distinct disciple.

Isbister and Bies [36] have also discussed why mathematical models have not gained broad acceptation in pharmacology, also applicable to cancer. They claim that *the mention of population analysis or pharmacokinetic and pharmacodynamic (PKPD) modelling often sends clinicians and clinical pharmacologists running, not wanting to know about mathematics and understanding complexity. Individualized dosing, optimal design of studies and mechanistic models of physiological processes are all 'too hard'*.

Our modern society relies on advanced technology, but we only apply it as common users (ie, GPS) and not struggling to understand it. If we want to advance, some clinicians need involved in this kind of research. We have to show our respective ignorance -mathematicians and biomedical scientists- and engage in a single group, trying to build a common knowledge.

2.3 Applied mathematicians do not care (much) about applications

Most mathematical researchers work in universities or academic research centers. This is also the case for those working on the mathematical analysis of models inspired by cancer. This usually means that their work is evaluated by their published production in mathematical journals (in general the purer, the better). In this context, the practical relevance of a result is not a criterion of excellence but a distraction taking time from academically rewarding activities. Morris Kline wrote: *What, then, should professors, especially young people who have yet to earn rank and tenure, publish? The obvious answer is to pick some specialty in pure mathematics and to invent problems that can be solved* [37].

Mathematics, like other sciences, has expanded enormously and most mathematicians are forced to focus on limited areas in order to keep abreast of other people's creations and produce new results of their own. The training of mathematicians, which is conducted by professors who are themselves specialists in narrow fields, follows the same course. Thus, students become experts on (and limited to) tools designed to deal with specific types of (sub)-problems. In some sense they may be 'trapped' into working on problems that can be solved using those tools. However, mathematical efforts with scientific goals related to the real world, require extensive background work because the subjects involved have been explored for many years.

Specifically, the so-called field of 'mathematics of cancer' requires a substantial medical and biological background. The bottom line is that few mathematicians are willing to do the hard work, also less productive academically, of moving into real mathematical applications to oncology, i.e. so-called *mathematical oncology*.

2.4 Holism vs. reductionism in mathematical modeling

Building good mathematical models of human diseases is a very difficult task, sometimes referred to as an 'art' because of its creative nature. There are no rules to construct a good model other than understanding qualitatively the dynamics of the system studied and being able to identify the key variables able to describe it at a certain scale. Thus, applied mathematical models are constrained by the biological knowledge available of a specific system.

Since a mathematical model is a simplification of reality, it is never perfect. However, a "correct" cancer model cannot be obtained by excessive elaboration. *Just as the ability to devise simple but evocative models is the signature of the great scientist so overelaboration and overparameterization is often the mark of mediocrity* [38]. However, many papers containing mathematical models related to cancer follow this pattern and include tens or even hundreds of unknown parameters (see e.g. the reviews [6, 10] and references therein). This makes many models useless since they can fit whatever kind of behavior is observed, but lack real predictive power. As John Von Neumann said: *With four parameters I can fit an elephant, and with five I can make him wiggle his trunk* [39]. This is refered to as 'overfitting' and has been discussed to be a problem of complex models in cancer [28, 36, 40, 41].

In building mathematical models of cancer we can learn a lot from the history of Physics and other quantitative sciences. The basic understanding of a system always comes first. Simple laws of fluid motion in tubes where written 300 years ago by Bernouilli, but some of those laws are still used in engineering. Today, we know that in many scenarios fluids are better approximated by more sophisticated models. However, those old simple laws are still used in practice by engineers.

Building simple mathematical models involves some kind of reductionism. This is different from the so-called systems biology approach. Systems biology refers to the computational and mathematical modeling of complex interactions within biological systems, using a holistic approach (i.e. holism instead of the more traditional reductionism) to biological research. One of the overarching aims of systems biology is to model and discover emergent properties of cells, tissues and organisms functioning as a system. The techniques which fall under the remit of systems biology typically involve metabolic networks or cell signaling networks, such as for example the enzymes and metabolites in a metabolic pathway. This leads to coupled systems with many differential (or algebraic) equations and up to hundreds of parameters [10, 42].

It is an interesting phenomenon that the community of mathematicians working on cancer models is almost non-intersecting in terms of conferences and scientific journals with the community of systems biology researchers. The former are usually educated as mathematicians while the latter are biologists or computational biologists. Also their interests are different: the former are more interested in the description of 'global' tissue properties while the latter typically focus on molecular and/or cellular processes.

The systems biology approach may be interesting for problems requiring a detailed understanding of complex processes with many relevant agents such as metabolism, etc. Indeed, more collaboration is required between both communities. However, the limited amount of information available on cancer patients makes the reductionist approach -the one that is used in most fields of quantitative sciences- more likely to be useful in the short and medium term.

2.5 Oversimplifying problems (or missing the point)

Using simple mathematical models does not mean oversimplifying cancer. Cancer is a complex disease involving many different elements [43]. First, cancer is not a single disease but a family of diseases. To be really useful mathematical models might have to focus on specific tumor types or particular characterstics shared by tumors. Moreover, cancer's clinical management involves typically the cooperation of several medical departments. Pathologists analyze biopsies and make the final diagnoses. Radiologists image the tumor in order to show its location and extension, helping to plan treatment and/or to monitor its response to therapies. Medical oncologists use chemotherapies to kill, neutralize or prevent dissemination of tumor cells. Radiation oncologists use ionizing radiations, either external or internal, for the same purpose with the support of medical physicists, typically in charge of radiation distribution and dosing questions. Surgeons, either general or specialized (such as neuro-surgeons) try to eradicate as much disease as possible and provide tumor tissue for histological and genetic diagnosis. Nuclear medicine is involved in the use of nuclear isotopes to image not only function but tumor metabolism and proliferation status. Finally other medical specialists work on specific cancers depending on their location.

Such a complex disease cannot be described completely by models that are too simple. In fact, this is one of the major criticisms made by biologists to mathematical models. They are typically trained to consider all the complexities of a system; however, the mathematical modeler should try to integrate the essential knowledge into simplified -but not trivial- models in order to understand the essentials. As Einstein said: "everything should be made as simple as possible, but not simpler".

It can also happen that even using very complex models one misses a relevant aspect of the system -sometimes also unknown to bioscientists-. For instance, a topic of enormous interest in Oncology, studied by mathematicians, has been the development of resistances. Many mathematical models have been constructed describing the system as the competition of two subpopulations: sensitive and resistant cells. These models assume that the dominant mechanisms ruling the competition are selection of more resistant cells (inherent chemoresistance) and induction of new resistant mechanisms by the therapies (induced chemoresistance) [44–46]. However, it has only recently become known that resistant cells secrete factors that makes sensitive cells refractory to the treatment. This has been later incorporated into mathematical models [47, 48]. In addition, new interaction phenomena have been observed between both cell subpopulations that cannot be explained using any of the previously existing models [49]. This means that even when many details are provided in the non-essential part of a mathematical model, the lack of knowledge of an essential part of it may preclude the model's applicability and usefulness.

2.6 Clinical data at the beginning and the end of any fruitful mathematical oncology story

Stakeholders in mathematical oncology share some elements of the agenda of the so-called precision medicine. The recent announcement of the Precision Medicine (PM) Initiative in the USA has brought PM to the forefront for healthcare providers, researchers, regulators, innovators, and funders alike. As technologies continue to evolve and datasets grow in magnitude, a strong computational and mathematical infrastructure will be essential

to realize PMs vision of improved healthcare derived from personal data [50]. Some mathematical models may require that kind of extensive information but others may be useful even when not being so 'precise'. Sometimes it may suffice pulling up and looking for physiological characteristics integrating molecular data at larger scales.

In order to do that, the applied mathematician has to start by understanding that the data are limited, incomplete, subject to many sources of error and sometimes incorrect. A relevant outcome of the interdisiciplinary collaboration must be to obtain quantitative data to validate the models. In cancer, information comes from different sources. Ancillary oncological care relies on biopsies. Biopsies allow valuable information to be obtained using inmuno-histochemistry, genomics, proteomics, metabolomics, etc. However, this information is constrained in space and time and usually pathological slides contain non-quantified information. Although digitized, its analysis relies on basic imaging techniques. It has been proposed that, using automated image analysis techniques, more precise information regarding intratumoral heterogeneity could be obtained [51]. Those observations could be integrated using quantitative, spatially explicit methods developed in landscape ecology to interrogate heterogeneous biological processes in tumors within individual patients. Although this is an interesting concept for the future, intratumor heterogeneity cannot be still fully sampled with most updated biopsies, even with genomic analysis [52] and in any case this would still provide static snapshots that may not describe real dynamics.

Non-invasive imaging (mainly CT, MRI and PET) fulfill this gap with temporal resolution. However, spatial resolution in clinical imaging is approximately 1 mm, that may be enough for studying certain aspects of tumoral heterogeneity [53].

For the applied mathematician images are numbers and contain a great deal of quantitative information, that is not easy to obtain by the naked eye. This information is dependent on the device characteristics, acquisition protocols and parameters. There is an effort at standardization in the clinics in order to make numbers comparable and thus more meaningful in multicenter clinical trials (e.g. in brain tumors [54]). Once the image is acquired, the different tumor compartments are to be separated (tumor segmentation), which leads to another source of discrepancies depending on the specific approach and/or the type of imaging considered (see e.g. [55, 56] for brain tumors). From the mathematical point of view it is necessary to define meaningful and robust measures of volumes, geometries, textures, etc., to be computed on images providing biomarkers of clinical relevance. Also, images are to be used as initial data for predictive mathematical algorithms able to simulate tumor evolution and provide therapy personalization.

Another source of information are blood tests, which allow clinically relevant biomarkers (such as e.g. PSA levels in prostate cancer) to be directly measured. In recent years the enthusiasm for so-called liquid biopsies to monitor cancer genetics through the analysis of circulating cells, nucleic acids or extracellular vesicles released from the tumor has grown dramatically [57, 58].

In addition to these sources of quantifiable information, there are many other data that are more qualitative, such as the different metrics of response or tumor progression (see e.g. [59] for brain tumors), symptoms, side effects, patient performance status, etc.

All of these data are invaluable for the development, testing and application of mathematical models and more importantly, for testing the applicability of such models. We cannot know if any mathematical model is useful unless we try to describe the real system with it. Thus, models need to be confronted with the information available from the tumor under study accounting for the constraints imposed by anatomy, physiology, energetics, etc. In fact, this is one of the reasons why mathematical models have found no real use in cancer treatment: most mathematical papers are purely theoretical and there is no confrontation with the known facts of the system supposedly being described by the model. First, the conception of the model has to be based on current knowledge. Second, it has to be consistent with data. Typically one would expect the model predictions to be tested on available information (i.e., existing databases), in the context of retrospective studies. There is a lot of information already available on the many clinical trials and studies already made on cancer that can be used for that purpouse. If model's predictions are validated with different data, prospective studies could be performed, provided the model's predictions are of clinical relevance [60].

2.7 Focus is not on relevant problems

More relevant than the mathematical model to be used is to determine the specific question that wants to be answered using the model. This is the main issue where the collaboration of oncologists is essential if we want to make an impact in the clinical management of patients. The oncologist knows the specific cancer type and the relevant question for any particular patient: What treatment should I try first? How shall I combine the therapies? Which patient should receive each therapy and in which dose? How can I combine different imaging techniques to understand what is going on? These are examples of the really relevant questions, the ones that, if answered, may lead to real progress in oncology.

Of course, not every cancer-related question can be solved using a mathematical model. Finding the right one is the result of discussions between biomedical scientists and mathematicians. Interestingly, a great deal of the mathematical publications motivated by oncology deal with the analysis (existence, uniqueness, properties of solutions, ...) of pre-existing (and sometimes useless) models than in developing key tools to solve clinically-motivated questions. Because of the enormous number of different cancer types, possible phenomena to include in the models, etc., it is very difficult for any modeling that is not driven by relevant questions to lead to significant therapeutic achievements.

It was John Synge who wrote: "Nature will throw out mighty problems but they will never reach the mathematician. He may sit in his ivory tower waiting for the enemy with an arsenal of guns, but the enemy will never come to him. Nature does not offer her problems ready formulated. They must be dug up with pick and shovel, and he who will not soil his hands will never see them" [61].

Life is not simple. Finding the good problems to address takes time and a lot of collaborative effort between mathematicians and clinicians, but it pays off later. Even a very partial answer to a relevant question, no matter how mathematically 'simple' the methods used, can be of great help in the war on cancer.

2.8 The problem of funding

Projects in the field of mathematical oncology are to be truly interdisciplinary in order to be useful. However a substantial content of applications may make projects seem 'too practical' for mathematical funding programmes in many countries. Also, a substantial content of mathematics may make project's look too theoretical for clinical funding programmes, or too non-standard for biologically-focused programmes. As with many interdisciplinary fields, projects in mathematical oncology may be under-rated and not funded [62]. This may make difficult for successful scientists to go out of their comfort zone of more classical research and get into this promising field.

Many public, both in the USA [63] and EU (see e.g. [64] and some projects funded within the current framework programme), and private (see e.g. [65]) initiatives are recognizing this problem and trying to solve it in different ways, but there is probably a long way to go.

As to the pharmaceutical industry, it has long recognized the need for a quantitative understanding of underlying pathways in drug discovery and clinical development [66]. This includes the use of systems biology, modelling and simulation as emerging tools potentially increasing the efficiency and productivity of new drug development. However, the initial interests of applied mathematicians and pharmaceutical companies are usually divergent. A lot of communication is necessary to initiate projects of interest for both communities, and more importantly, cancer patients.

In general, mathematical research is very cheap in comparison to most other experimental fields. The returns in investment are expected to be huge for the scales of biomedical reasearch even when modest improvements due to the mathematical work are achieved. The fact that mathematical models are dynamical, interactive and potentially able to describe phenomena hard to mimick in animal models with arficial contexts may lead to substantial advances, enormous savings of money and/or great benefits for patients.

3 What can be expected from mathematics

There are many ways applied mathematics -beyond statistics- can be useful in oncology as they have been in many other branches of science. In this section we discuss some of them.

3.1 Approach oncology in a systematic and rigorous way

Historically, in the rise of many disciplines as solid bodies of scientific knowledge, mathematicians have been the driving force. *He (the mathematician) insisted that thought be logical. As each new science came up, he gave it the firm logical structure that Euclid gave to Egyptian land surveying. A subject came to his hands a rough stone, trailing irrelevant weeds; it left his hands a polished gem* [61].

This has not been the case in life sciences, since those fields grew up been mostly observational and still mostly lack the same kind of formalization othes disciplines have. Life scientists are not so used as applied mathematicians to building precise (i.e. mechanistic) closed conceptual frameworks. They are also not familiar with how complex dynamics can arise from nonlinear feedback loops even with few relevant variables. It is customary to think of complex dynamics as the result of the interplay of many factors. However, complex dynamics can arise even in simple models depending on the nonlinear interplay of the most relevant variables as it is well known in nonlinear sciences and specifically in the context of chaos theory [67–69]. The mathematical modeler is trained to understand the essentials of a process or phenomenon. Sometimes, this understanding requires more data. The mathematician may ask for data to help in defining the model. Sometimes, this is not the same type of data the biomedical scientist thinks of as being relevant to understand the system under study.

In this regard, mathematicians may help life scientists to better understand their experimental findings. Namely, life scientists usually think in a linear manner i.e. if they silence this gene expression, the level of its protein product will decrease and this will induce the blockage of a certain cellular process. In an experimental setting, they need to check the level of other components involved in the regulation of the specific process and thus include many variables. Considering the cost of the experimental work, this can be performed only in one or two model systems in the same laboratory. After publication of these findings, other researchers may examine the concept on different experimental models and confirm or rebut it. Unambiguous explanation of the phenomenon with many variables involved may lead to wrong conclusion. Therefore, implementation of mathematical non-linear way of thinking is essential for the progress in life science and particularly cancer research that need to be achieved in future.

3.2 Raising novel hypotheses

Mathematical models are simplifications of reality allowing the behavior of a system to be reproduced, but they also provide ways to raise novel hypotheses. If a model is 'correct' to a certain extent, one may ask the model questions that may lead to unexpected answers. This methodology opens novel possibilities in Oncology since one cannot, due to ethical reasons, deviate radically from the standard clinical practice, test every possible fractionation or combinatorial treatment scheme, etc.

As examples in neuro-oncology we would like to cite several recent studies. The first used a mathematical model to predict that brain tumors could be classified according to the size of the tumor bulk (measured using the T1-weighted MRI sequence) in relation to the size of the infiltrative component (measured on MRI using the T2 sequence) [25]. Interestingly this allowed tumors to be classified as nodular or infiltrative and predicted which ones (the nodular ones) would benefit more from radical surgery. The predictions were verified using retrospective data. Another example comes from a different model [70] that hypothesized that some measures of the tumor's geometry obtained from post-contrast, T1-weighted images, would provide estimates of the tumor infiltration speed and aggressiveness. Using retrospective data, the predictions were validated in Ref. [27]. These novel measures (or imaging biomarkers, using the medical terminology), turned out to be powerful predictors of survival, better indeed than classical, more 'reasonable' variables, such as tumor volume. They also were found useful to predict the response to antiangiogenic therapies before treatment [71]. Finally, we would like to

mention Ref. [72] where it was hypothesized that the combination of antioxidants with cytotoxic therapies would provide a substantial survival benefit. The mathematical model was validated in microfluidic chips [73, 74], the predictions found to be valid in experiments in cell lines and animal models [75]. Even more importantly, a clinical trial is being planned based on this model. Another example based on a mathematical model, this time in breast cancer, allowed to hypothesized that exploiting evolutionary principles may prolong tumor control in preclinical models [76]. The concepts have led to an ongoing clinical trial in castration resistant prostate cancer treated with abiraterone [77]. These are only examples, but indicative of a rising tide of real applications coming from hypotheses originated in mathematical models.

We think that generating hypotheses is the major potential contribution of applied mathematics to Oncology, with many other examples to come in the future. This philosophy gives up in trying to describe with a few percent precision the behavior of every variable involved. Instead, the mathematical model provides a conceptual framework able to understand the phenomena under study and allows general predictions on the system behavior to be made. These predictions can later be validated experimentally. In this way, models, albeit incomplete, may lead to substantial scientific advances as it was summarized by G. Box in his famous sentence: *All models are wrong, but some are useful* [38].

3.3 Personalizing therapies

Personalized medicine aims to separate patients into different groups with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease. The terms personalized medicine, precision medicine, stratified medicine and P4 medicine are used interchangeably to describe this concept though some authors use these expressions separately to indicate particular nuances.

While the tailoring of treatment to patients dates back at least to the time of Hippocrates, the term has increased in usage in recent years given the growth of new diagnostic and informatics approaches that provide understanding of the molecular basis of disease, particularly genomics. Despite the promises of personalized cancer treatments, not all types of cancer have personalized treatment options. Mathematical models of cancer have been publicized as having the potential to tailor treatments to individual patients. As described in Sec. 3.2 this may be the case for particular patient subgroups (as happens routinely with other biomarkers). Individualizing treatments to a greater extent would involve a perfect identification of model parameters for each patient, something that is very difficult to do on the basis of the limited information available from medical imaging, biopsies, and other data sources.

The final goal of the personalization philosophy would be mathematical models to provide an 'in-silico twin' [78, 79] that would allow, once parameters are identified, to personalize anti-cancer therapies. This is a very relevant objective although more work is necessary to make it real. As an example, a non-trivial radiotherapy fractionation was found in Ref. [80] to improve efficacy of radiotherapy treatment of a specific type of brain tumor. Using their model, the authors identified two delivery schedules predicted to significantly improve efficacy by taking advantage of the dynamic instability of radio-resistance. These schedules led to superior survival in mice. However, fitting the sixteen model parameters required studying the response in many identical mice. Obviously, these results cannot be directly translated to the clinics as usually there are no copies of a patient available to find his parameters. However, if 'in-silico' twins are ever available they may provide a way to optimize even classical therapies to obtain substantial improvements in survival.

More work is necessary to develop non-invasive techniques providing more information on the extent, biology and heterogeneity of tumors. High resolution MRI's, positron emission tomography (PET) techniques with improved spatial resolution, liquid biopsies (see e.g. [54, 81, 82] for examples in Neuro-oncology) and probably other methodologies may be necessary to feed mathematical models with data allowing to personalize therapies.

3.4 In-silico clinical trials

The traditional model for the development of medical treatments and devices begins with pre-clinical development. In laboratories, test-tube and other in vitro experiments establish the plausibility for the efficacy of the treatment. Then in vivo animal models, with different species, provide guidance on the efficacy and safety of the product for humans. Finally, clinical trials are mandatory to test whether the product may be made available to humans. Clinical trials are often divided into four phases. Phase 3 involves testing a large number of people. When a medication fails at this stage, the financial losses can be catastrophic.

The fundamental nature of clinical trials has changed surprisingly little in recent centuries. Predictive mathematical models allow the investigation of living organisms through computer simulations, (also called in silico medicine). Thus, an in silico clinical trial is an individualized computer simulation used in the development or regulatory evaluation of a medicinal product, device, or intervention. While completely simulated clinical trials are not feasible with current technology and understanding of biology, its development would be expected to provide major benefits over current in vivo clinical trials, and research into it is being pursued. A European strategy for in-silico clinical trials is being developed [83]. One of their potential uses is narrowing down the number of key variables in the standard clinical trials and, very importantly, significantly reduce their economic cost and patient burden.

There is still a long way to go before this concept can be used in cancer research, if it is ever used.

4 Conclusions: Why mathematicians are needed in the war on cancer

The only way to develop successful interdisciplinary collaborations is to create and nurture communicative and interactive platforms allowing the regular meeting of mathematicians and clinicians and/or biomedical scientists. For the mathematician, this may help to acquire the necessary knowledge together with an understanding of the complexity of the problems under study, the extent of available data and to learn the medical language. For clinicians and bioscientists this is required to understand the potential of the mathematical tools which could speed up preclinical study as well as clinical trials. Although the situation is changing, there is still little cross-talk between clinicians and bioscientists and their mathematical colleagues.

Nevertheless, we are convinced that these conversations would help to identify the problems to be addressed and to work on the mathematical models that could tackle them. As discussed before, developing the model first and then looking for the question to answer using it is almost never going to work.

Despite billions of dollars being spent, and some of the world's best brains being hard at work, cancer has not been beaten. Different approaches complementing classical ones are required. One of them may be to increase the use of tools offered by applied mathematics and nonlinear sciences. Mathematicians have a unique set of skills that may be very useful, even essential, in the war on cancer. They understand complex systems both nonlinear and stochastic, they truly recognize what is required to make causal claims and understand that "reducing" a system may be the best way to handle it without any loss of essential information.

The time may be right for bringing mathematicians and cancer researchers together to create new opportunities to move treatments away from the traditional static and linear approaches to tumor biology and by working in sync maybe produce a new generation of researchers and clinicians who naturally come together.

Cancer patients deserve the best of our minds and in the future it could be ourselves who are affected by the disease.

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